

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) Publication number:

**0 531 823 A1**

(12)

**EUROPEAN PATENT APPLICATION**(21) Application number: **92114691.6**(22) Date of filing: **28.08.92**

(51) Int. Cl.<sup>5</sup>: **C07D 311/22, C07D 311/24, C07D 407/12, C07D 307/83, C07D 311/76, C07D 405/12, C07C 57/50, A61K 31/35, A61K 31/34, A61K 31/185**

(30) Priority: **10.09.91 US 757100**  
**15.06.92 US 898852**

(43) Date of publication of application:  
**17.03.93 Bulletin 93/11**

(84) Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE**

(71) Applicant: **F. HOFFMANN-LA ROCHE AG**  
**Postfach 3255**  
**CH-4002 Basel(CH)**

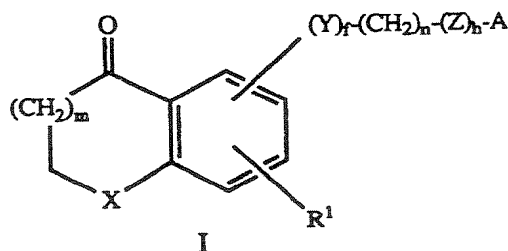
(72) Inventor: **Cohen, Noal**

**19 Euclid Place**  
**Montclair, N.J. 07042(US)**  
Inventor: **Lee, Ferdinand Kwo-chen**  
**100 Fycke Lane**  
**Teaneck, N.J. 07666(US)**  
Inventor: **Yagaloff, Keith Alan**  
**10 Loyd Road**  
**Hohokus, N.J. 07423(US)**

(74) Representative: **Kellenberger, Marcus, Dr. et al**  
**Grenzacherstrasse 124 Postfach 3255**  
**CH-4002 Basel (CH)**

(54) **Bicyclic carboxylic acid derivatives as anti-inflammatory agents.**

(57) Compounds of the formula



wherein

X is -O- or -CH<sub>2</sub>-;

Y is -O-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C- or -OCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-;

Z is -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -C≡C-;

R<sup>1</sup> is hydrogen, lower alkyl, lower alkenyl, cycloalkyl or aralkyl;

A is -B or -O-B;

B is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group -COR<sup>2</sup>, -(O)<sub>t</sub>-(W)<sub>s</sub>-COR<sup>2</sup> or -(CH=CH)<sub>p</sub>COR<sup>2</sup> and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)<sub>k</sub>-(W)<sub>s</sub>-E

**EP 0 531 823 A1**

or  $-(Q)_k-(W)_{s''}-$

$C_6H_4-(W)_{s'''}-E$ , provided that no more than one of said substituents is  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_{s''}-C_6H_4-(W)_{s'''}-E$ ;

$E$  is  $-COR^2$  or  $R^2$ ;

$W$  is  $-CR^3R^4-$ ;

$Q$  is  $-O-$  or carbonyl;

$R^2$  is hydroxy, lower alkoxy or  $-NR^3R^4$ ;

$R^3$  and  $R^4$ , each occurrence, independently, are hydrogen or lower alkyl;

$f$ ,  $h$ ,  $k$ ,  $m$  and  $t$ , independently, are 0 or 1;

$n$ ,  $s$  and  $s'$ , independently, are an integer from 1 to 12;

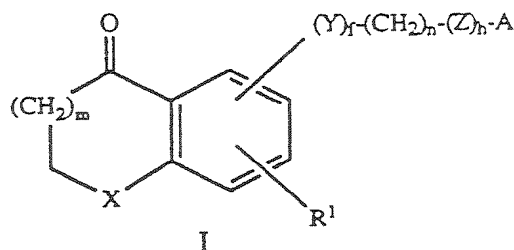
$p$  is an integer from 1 to 2;

$s''$  and  $s'''$ , independently, are an integer from 0 to 12; and

$C_6H_4$  is a 1,2-, 1,3- or 1,4-phenylene moiety.

their geometric and optical isomers and, when  $R^2$  hydroxy, pharmaceutically acceptable salts thereof with bases are potent leukotriene  $B_4$  antagonists and are therefore useful in the treatment of inflammatory diseases, such as psoriasis, inflammatory bowel diseases, asthma, allergy, arthritis, dermatitis, gout, pulmonary disease, ischemia/reperfusion injury, and trauma induced inflammation, such as spinal cord injury.

The present invention relates to compounds of the general formula



wherein

X is -O- or -CH<sub>2</sub>-;

Y is -O-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C- or -OCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-;

Z is -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -C≡C-;

R<sup>1</sup> is hydrogen, lower alkyl, lower alkenyl, cycloalkyl or aralkyl;

A is -B or -O-B;

B is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group -COR<sup>2</sup>, -(O)<sub>t</sub>-(W)<sub>s</sub>-COR<sup>2</sup> or -(CH=CH)<sub>p</sub>COR<sup>2</sup> and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)<sub>k</sub>-(W)<sub>s</sub>-E or -(Q)<sub>k</sub>-(W)<sub>s</sub>-

C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E, provided that no more than one of said substituents is -(Q)<sub>k</sub>-(W)<sub>s</sub>-E or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E;

E is -COR<sup>2</sup> or R<sup>2</sup>;

W is -CR<sup>3</sup>R<sup>4</sup>-;

Q is -O- or carbonyl;

R<sup>2</sup> is hydroxy, lower alkoxy or -NR<sup>3</sup>R<sup>4</sup>;

R<sup>3</sup> and R<sup>4</sup>, each occurrence, independently, are hydrogen or lower alkyl;

f, h, k, m and t, independently, are 0 or 1;

n, s and s', independently, are an integer from 1 to 12;

p is an integer from 1 to 2;

s'' and s''', independently, are an integer from 0 to 12; and

C<sub>6</sub>H<sub>4</sub> is a 1,2-, 1,3- or 1,4-phenylene moiety,

their geometric and optical isomers and, when R<sup>2</sup> is hydroxy, pharmaceutically acceptable salts thereof with bases.

These compounds are potent leukotriene B<sub>4</sub> antagonists and are therefore useful in the treatment of inflammatory diseases, such as psoriasis, inflammatory bowel disease, asthma, allergy, arthritis, dermatitis, gout, pulmonary disease, ischemia/reperfusion injury and induced inflammation, such as spinal cord injury.

Objects of the present invention are the compounds of formula I and their pharmaceutically acceptable salts per se and for use as therapeutically active substances, the manufacture of these compounds, medicaments containing these and the manufacture of such medicaments, as well as the use of compounds of formula I and their pharmaceutically acceptable salts in the control or prevention of illnesses or in the improvement of health, especially in the control or prevention of inflammatory diseases, such as psoriasis, inflammatory bowel disease, asthma, allergy, arthritis, dermatitis, gout, pulmonary disease, ischemia/reperfusion injury and induced inflammation, such as spinal cord injury.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl", denotes a straight or branched chain saturated hydrocarbon containing 1 to 7 carbon atoms, preferably from 1 to 4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, neopentyl, pentyl, heptyl and the like. The term "lower alkoxy" denotes an alkyl ether group in which the alkyl group is as described above, for example, methoxy, ethoxy, propoxy, pentoxy and the like.

The term "cycloalkyl" denotes a cyclic alkyl group of 3 to 6 carbon atoms, for example, cyclopropyl, cyclohexyl and the like.

The term "lower alkenyl" denotes a straight or branched chain unsaturated hydrocarbon containing 2 to 7 carbon atoms, for example, vinyl, propenyl, butenyl and the like.

The term "halogen" denotes the four halogens bromine, chlorine, fluorine and iodine. The term "aryl" or "mono-, di- or tricyclic aromatic" preferably denotes naphthalenyl, phenyl, anthracenyl, phenathrenyl or the like, which may be mono-, di- or trisubstituted by halogen, trifluoromethyl, lower alkyl, phenyl, lower alkoxy, cyano or nitro.

5 The term "aralkyl" denotes an alkyl group substituted by an aryl group, for example, benzyl, phenethyl or the like, which may be substituted by halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, nitro or the like.

The term "lower alkanoyl" denotes a primary or secondary alkanoyl group containing up to 7 carbon atoms such as acetyl, propionyl, butyryl, isobutyryl and the like. The term "aroyl" preferably denotes the 10 benzoyl group or a substituted benzoyl group, for example a nitrobenzoyl group such as p-nitrobenzoyl or a halobenzoyl group such as o-, m- or p-iodobenzoyl.

The term "heteroaromatic moiety" denotes a monocyclic 5- or 6- membered heterocyclic or a bi- or tricyclic heterocyclic radical containing one or more hetero atoms selected from nitrogen, oxygen and sulfur which radical may optionally be, independently, substituted by one or two substituents selected from lower 15 alkyl, lower alkoxy, chlorine and fluorine. It is understood that heterocyclic refers to a carbocyclic moiety in which one or more of the carbons are replaced, independently, by oxygen, nitrogen or sulfur.

Exemplary of 5- or 6- membered aromatic heteromonocyclic radicals are pyridinyl, imidazolinyl, thienyl, 2-chlorothieryl, furyl, pyrimidinyl, oxazolanyl or the like.

Exemplary of hetero-bicyclic radicals are benzofuranyl, benzopyranyl, indolyl, quinolanyl, benzothienyl 20 or the like.

Exemplary of hetero-tricyclic radicals are dibenzofuranyl, carbazoyl or the like.

Exemplary of the group  $-(W)_{-s,s',s'' \text{ or } s'''}-$ , that is,  $-(CR^3R^4)_{-s,s',s'' \text{ or } s'''}-$  are 1,1-dimethylpropylenyl, 2,2-dimethylpropylenyl, 2,6-dimethylheptylenyl, 1-methyl-1-ethylpentylenyl, 1-ethyl-3-methylhexylenyl or the like.

As used herein, a leaving group denotes halogen, preferably bromine and iodine lower alkylsulfonyloxy 25 such as methylsulfonyloxy, trifluoromethylsulfonyloxy or the like, arylsulfonyloxy such as para-toluenesulfonyloxy or the like.

A particular group of compounds of formula I is one in which E is  $-\text{COR}^2$ .

A preferred, group of compounds of formula I is one in which Y is  $-\text{O}-$ ,  $\text{R}^1$  is lower alkyl, n is 3-8 and m and f are 1.

30 A more preferred group of compounds of formula I is one in which Y is  $-\text{O}-$ ,  $\text{R}^1$  is lower alkyl, h is 0, m and f are 1, n is 3-8 and A is  $-\text{O}-\text{B}$ , and B is a mono-, di- or tricyclic aromatic moiety.

A still more preferred group of compounds of formula I is one in which Y is  $-\text{O}-$ ,  $\text{R}^1$  is lower alkyl or aralkyl, h is 0, m and f are 1, n is 3-8 and A is  $-\text{B}$ , wherein B is a monocyclic aromatic moiety, preferably phenyl, substituted by  $-(\text{O})_t$ ,  $-(W)_s$ ,  $-\text{COR}^2$  and  $-(Q)_k$ ,  $-(W)_s$ ,  $-\text{E}$ , wherein E is  $\text{COR}^2$ , Q is  $-\text{O}-$ ,  $\text{R}_2$  is hydroxy, t is 0, s is 2, k is 1 and s' is 1 to 12. 35

A most preferred group of compounds of formula I is one in which X and Y are  $-\text{O}-$ ,  $\text{R}^1$  is lower alkyl, h is 0, m and f are 1, n is 3-8 and A is  $-\text{B}$ , wherein B is a monocyclic aromatic moiety, preferably phenyl, substituted by  $-(\text{O})_t$ ,  $-(W)_s$ ,  $-\text{COR}^2$  and  $-(Q)_k$ ,  $-(W)_s$ ,  $-\text{E}$  wherein E is  $-\text{COR}^2$ , Q is  $-\text{O}-$ ,  $\text{R}_2$  is hydroxy, t is 0, s is 2, k is 1 and s' is 1 to 6.

40 Most preferred examples of this invention are:

2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid;

2-(4-Carboxybutoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid;

45 2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid;

2-[(4-Carboxy-4-methylpentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid;

50 5-(3-Carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid;

6-(4-Carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid;

E-3-[5-(3-Carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]phenyl]-2-propenoic acid;

55 3-(2-Carboxyethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepentanoic acid;

2-(2-Carboxyethyl)-3-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenehexanoic acid; 2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-6-[(5-hydroxypentyl)oxy]-



benzenepropanoic acid; and

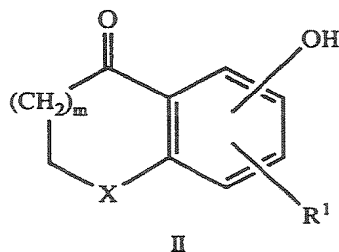
2-[(5-Carboxypentyl)oxy]-6-[6-[(5,6,7,8-tetrahydro-5-oxo-1-propyl-2-naphthalenyl)oxy]hexyl]-benzenepropanoic acid.

Preferred examples of this invention are:

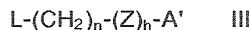
- 5 5-[(3-Carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid;
- 5-[(3-Carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid;
- 5-[(3-Carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyloxy]-benzenepropanoic acid;
- 10 5-(3-Carboxypropoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid;
- 5-(4-Carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid hemihydrate;
- 15 5-[(3-Carboxyphenyl)carbonyl]-2-[7-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]heptyloxy]-benzenepropanoic acid;
- 5-[(3-Carboxyphenyl)carbonyl]-2-[8-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]octyloxy]-benzenepropanoic acid;
- 5-[(4-Carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid;
- 20 3-(2-Carboxyethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]- $\gamma$ -oxobenzenebutanoic acid;
- 5-[2-(2-Carboxyphenyl)-1-oxoethyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid;
- 25 6-(Carboxymethoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-1-naphthalenepropanoic acid;
- 2-[[5-[(3,4-Dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepropanoic acid; and
- 2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid.
- 30 Other examples of this invention are:
- rac-6-Acetyl-7-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid;
- 5-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-2-benzofurancarboxylic acid;
- 6-[[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-2,5-quinolinedipropanoic acid;
- 35 2-[5-[(2,3-Dihydro-1-oxo-4-propyl-1H-inden-5-yl)oxy]pentyloxy]benzenepropanoic acid;
- (E)-3-[2-[7-(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-1,6-heptadiynyl]phenyl]-2-propenoic acid;
- 5-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-2-thiophenepropanoic acid;
- 4-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-3-thiophenepropanoic acid;
- 3-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-2-thiophenepropanoic acid;
- 40 2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-3-thiophenepropanoic acid;
- 2-[5-[(5-Oxo-2-propyl-5,6,7,8-tetrahydro-1-naphthalenyl)oxy]pentyloxy]benzenepropanoic acid;
- 2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-5-[(methylsulfonyl)amino]-benzenepropanoic acid;
- (E)-3-[5-Cyano-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]phenyl]-2-propenoic acid;
- 45 2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-5-(3-carboxypropoxy)-3,4,6-trimethylbenzenepropanoic acid;
- (E,E)-5-[2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]phenyl]-2,4-pentadienoic acid;
- 50 2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-6-[(5-aminopentyl)oxy]benzenepropanoic acid;
- 2-[(6-Dimethylamino-6-oxohexyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid and the like.

In accordance with the present invention, the compounds of formula I and their pharmaceutically acceptable salts can be prepared by a process which comprises

(a) for the manufacture of compounds of formula I wherein Y is -O-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy and the remaining symbols are as previously described, reacting a compound of the general formula

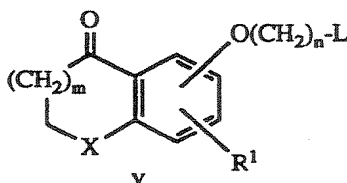


wherein X, R<sup>1</sup> and m are as previously described,  
with a compound of the general formula



wherein Z, h and n are as previously described, A' is -B' or -O-B', wherein B' is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group -COR<sup>2'</sup>, -(O)<sub>t</sub>(W)<sub>s</sub>COR<sup>2'</sup> or -(CH=CH)<sub>p</sub>COR<sup>2'</sup> and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)<sub>k</sub>-(W)<sub>s</sub>-E' or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E', provided that no more than one of said substituents is -(Q)<sub>k</sub>-(W)<sub>s</sub>-E' or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E', wherein E' is -COR<sup>2'</sup> or R<sup>2'</sup> and R<sup>2'</sup> is lower alkoxy and Q, W, C<sub>6</sub>H<sub>4</sub>, k, p, s, s', s'', s''' and t are as previously described, and L is a leaving group,

or  
(b) for the manufacture of compounds of formula I wherein Y is -O-, f is 1, A is -O-B and R<sup>2</sup> in symbol A is lower alkoxy and the remaining symbols are as previously described, reacting a compound of the general formula

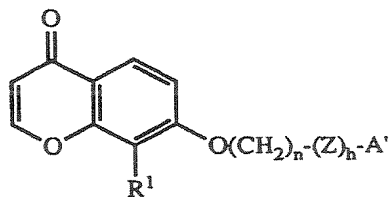


wherein X, R<sup>1</sup>, L, m and n are as previously described,  
with a compound of the general formula



wherein B' is as previously described,  
or

(c) for the manufacture of compounds of formula I wherein X and Y, independently, are -O-, f and m, independently, are 1 and R<sup>2</sup> in symbol A is lower alkoxy, with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, catalytically hydrogenating a compound of the general formula

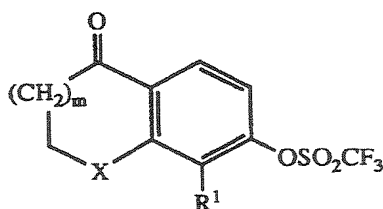


IX

wherein Z, R¹, A', h and n are as previously described,

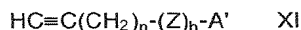
or

(d) for the manufacture of compounds of formula I wherein Y is  $-\text{C}\equiv\text{C}-$ , f is 1 and R² in symbol A is lower alkoxy, with R¹ being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, reacting a compound of the general formula



X

wherein X, R¹ and m are as previously described,  
with a compound of the general formula



wherein Z, A', h and n are as previously described,

or

(e) for the manufacture of compounds of formula I wherein Y is  $-\text{CH}_2\text{CH}_2-$ , f is 1 and R² in symbol A is lower alkoxy, with R¹ being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, catalytically hydrogenating a compound of formula I wherein Y is  $-\text{C}\equiv\text{C}-$ , f is 1 and R² in symbol A is lower alkoxy, with R¹ being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described,

or

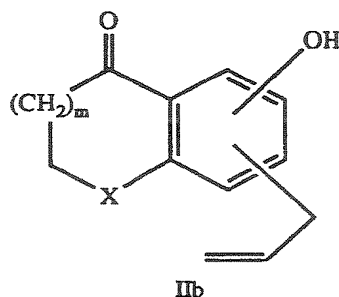
(f) for the manufacture of compounds of formula I wherein Y is  $-\text{O}-$ , f is 1 and R² in symbol A is hydroxy, and the remaining symbols are as previously described, saponifying a compound of formula I wherein Y is  $-\text{O}-$ , f is 1 and R² in symbol A is lower alkoxy, and the remaining symbols are as previously described,

or

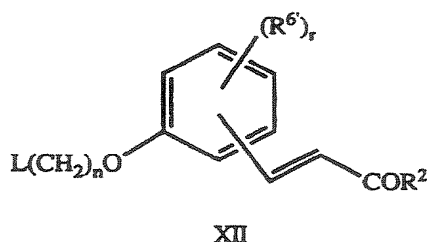
(g) for the manufacture of compounds of formula I wherein Y is  $-\text{C}\equiv\text{C}-$  or  $-\text{CH}_2\text{CH}_2-$ , f is 1 and R² in symbol A is hydroxy with R¹ being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, saponifying a compound of formula I wherein Y is  $-\text{C}\equiv\text{C}-$  or  $-\text{CH}_2\text{CH}_2-$ , f is 1 and R² in symbol A is lower alkoxy, with R¹ being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described,

or

(h) for the manufacture of compounds of formula I wherein Y is  $-\text{O}-$ , f is 1, h is zero, R¹ is allyl, A is  $-\text{O}-\text{B}$  and B is phenyl substituted by the group  $-\text{CH}=\text{CH}-\text{COR}^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(\text{Q})_k-(\text{W})_s-\text{E}$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}$ , provided that no more than one of said substituents is  $-(\text{Q})_k-(\text{W})_s-\text{E}$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}$ , with  $-\text{COR}^2$  being lower alkoxycarbonyl, and the remaining symbols are as previously described, reacting a compound of the general formula



wherein X and m are as previously described,  
with a compound of the general formula



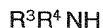
wherein  $R^2$ , L and n are as previously described and r is an integer from 0 to 4,  $R^6$ , each occurrence, independently, is halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E'$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E'$ , provided that no more than one of  $R^6$  is  $-(Q)_k-(W)_s-E'$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E'$ , wherein Q, W, E',  $C_6H_4$ , k, s', s'' and s''' are as previously described,

or

(i) for the manufacture of compounds of formula I wherein Y is -O-, f is 1, h is zero,  $R^1$  is propyl, A is -O-B and B is phenyl substituted by the group  $-CH_2CH_2-COR^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E$ , provided that no more than one of said substituents is  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E$ , with  $-COR^2$  being lower alkoxycarbonyl, and the remaining symbols are as previously described, catalytically hydrogenating a compound of formula I wherein Y is -O-, f is 1, h is zero,  $R^1$  is allyl, A is -O-B and B is phenyl substituted by the group  $-CH=CH-COR^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E$ , provided that no more than one of said substituents is  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E$ , with  $-COR^2$  being lower alkoxycarbonyl, and the remaining symbols are as previously described,

or

(k) for the manufacture of compounds of formula I wherein A is -B or -O-B, wherein B is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group  $-COR^2$ ,  $-(O)_1-(W)_s-COR^2$  or  $-(CH=CH)_pCOR^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E$ , provided that no more than one of said substituents is  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E$ , and wherein E is  $-COR^2$  and  $R^2$  is  $-NR^3R^4$  and  $R^3$  and  $R^4$ , each occurrence, independently, are hydrogen or lower alkyl and the remaining symbols are as previously described, treating a compound of formula I wherein A is -B or -O-B, wherein B is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group  $-COR^2$ ,  $-(O)_1-(W)_s-COR^2$  or  $-(CH=CH)_pCOR^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E$ , provided that no more than one of said substituents is  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E$ , and wherein E is  $-COR^2$  and  $R^2$  is hydroxy with an amine of the general formula

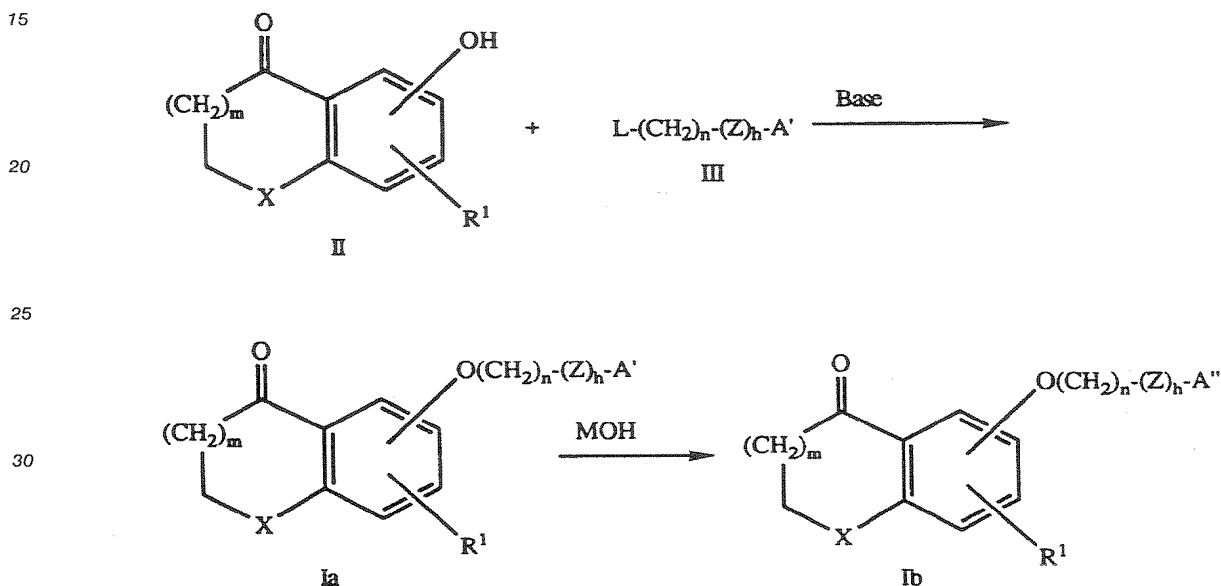


wherein  $R^3$  and  $R^4$  are as previously described,  
and, if desired,

(l) converting a compound obtained into a pharmaceutically acceptable salt.

5 The reaction conditions for the above process variants are described in more detail hereinafter in Reaction Schemes 1-6, 25 and 28. The starting materials can be prepared as described in Reaction Schemes 1 - 32 or in an analogous manner. The compounds of formulae II, III and VI are known compounds or can be prepared in an analogous manner as the known compounds.

## Reaction Scheme 1



wherein  $A'$  is  $-B'$  or  $-O-B'$ , wherein  $B'$  is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group  $-COR^{2'}$ ,  $-(O)_t(W)_sCOR^{2'}$  or  $-(CH=CH)_pCOR^{2'}$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E'$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E'$ , provided that no more than one of said substituents is  $-(Q)_k-(W)_s-E'$ , or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E'$ ,  $E'$  is  $-COR^{2'}$  or  $R^{2'}$  and  $R^{2'}$  is lower alkoxy.

$A''$  is  $-B''$  or  $-O-B''$ , wherein  $B''$  is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group  $-COR^{2''}$ ,  $-(O)_t(W)_sCOR^{2''}$  or  $-(CH=CH)_pCOR^{2''}$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E''$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E''$ , provided that no more than one of said substituents is  $-(Q)_k-(W)_s-E''$ , or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E''$ ,  $E''$  is  $-COR^{2''}$  or  $R^{2''}$  and  $R^{2''}$  is hydroxy.

L is a leaving group, M is an alkali metal, and h, m, n, X, Z, and  $R^1$  are as previously described.

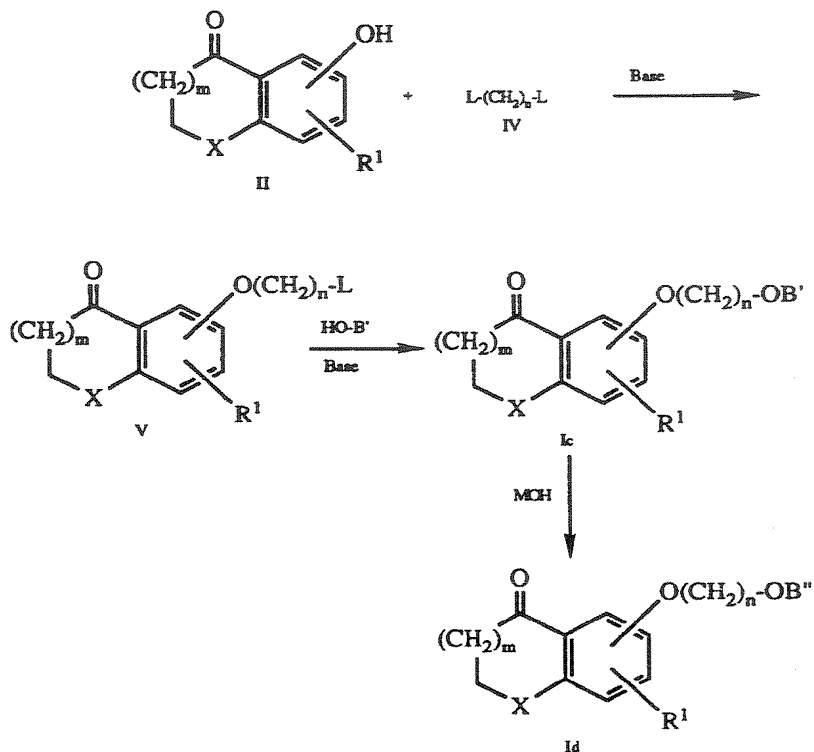
In Reaction Scheme 1, a compound of formula II, which represents known compounds or compounds which can be prepared according to known procedures or as hereinafter described, is allowed to react with a compound of formula III, which represents known compounds or compounds which can be prepared according to known procedures or as hereinafter described, in the presence of a base, for example, an alkali metal carbonate such as sodium or potassium carbonate, at a temperature in the range of from about 25 ° to about 110 ° C, in a polar, aprotic solvent such as acetonitrile, N,N-dimethylformamide, 2-butanone, dimethyl sulfoxide and the like.

Alternatively, the procedure of U.S. Patent No. 4,931,574 can be utilized. In this variation, compounds of formulae II and III are allowed to react in the presence of an alkali metal carbonate, preferably potassium carbonate, and a phase transfer catalyst preferably tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1), in an

aromatic hydrocarbon solvent, preferably toluene, at a temperature in the range of 80 ° to 110 ° C.

The resulting compound of formula Ia can be recovered utilizing conventional methods such as chromatography or recrystallization and can be converted by saponification using an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, in a solvent mixture of water and a water miscible solvent  
 5 such as methanol, ethanol or tetrahydrofuran, at a temperature in the range of from about 25 ° to about 60 ° C, to the corresponding acid of formula Ib. The compounds of formula Ib can be purified by conventional methods such as recrystallization, chromatography and the like.

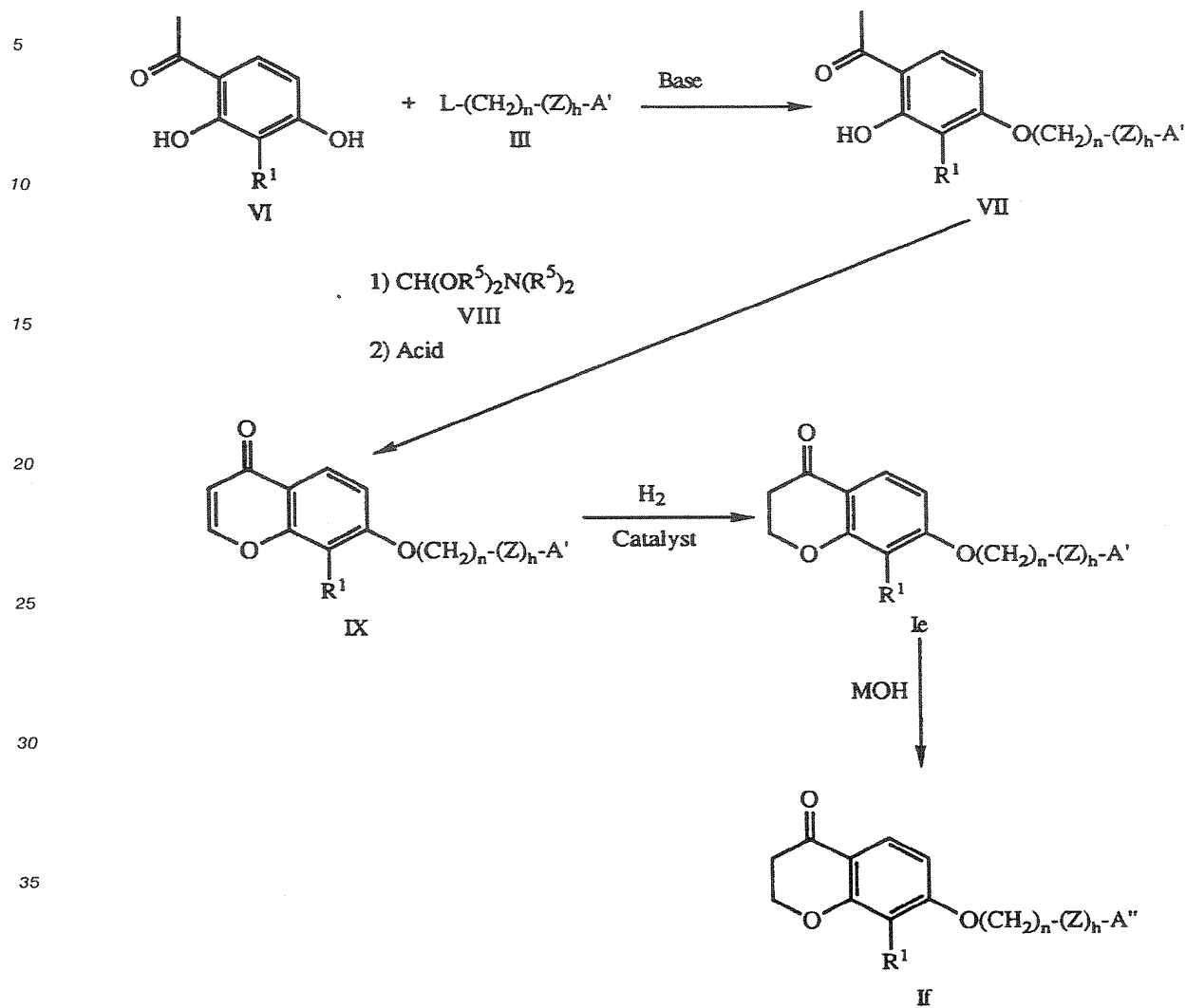
## Reaction Scheme 2



wherein B', B'', L, X, R<sup>1</sup>, M, m and n are as previously described.

In Reaction Scheme 2, a compound of formula II is allowed to react with a compound of formula IV which represents known compounds, in the presence of a base and under conditions as described in Reaction Scheme 1. The resulting compound of formula V can be recovered by conventional techniques  
 45 such as chromatography and is allowed to react with a compound of formula HO-B', in the presence of a base and under conditions as described in Reaction Scheme 1. The resulting compound of formula Ic is purified by conventional chromatography or recrystallization methods. Saponification of compound Ic under conditions described in Reaction Scheme 1 for the conversion of Ia to Ib gives the corresponding acid of formula Id which can be purified by aforementioned conventional procedures.

## Reaction Scheme 3

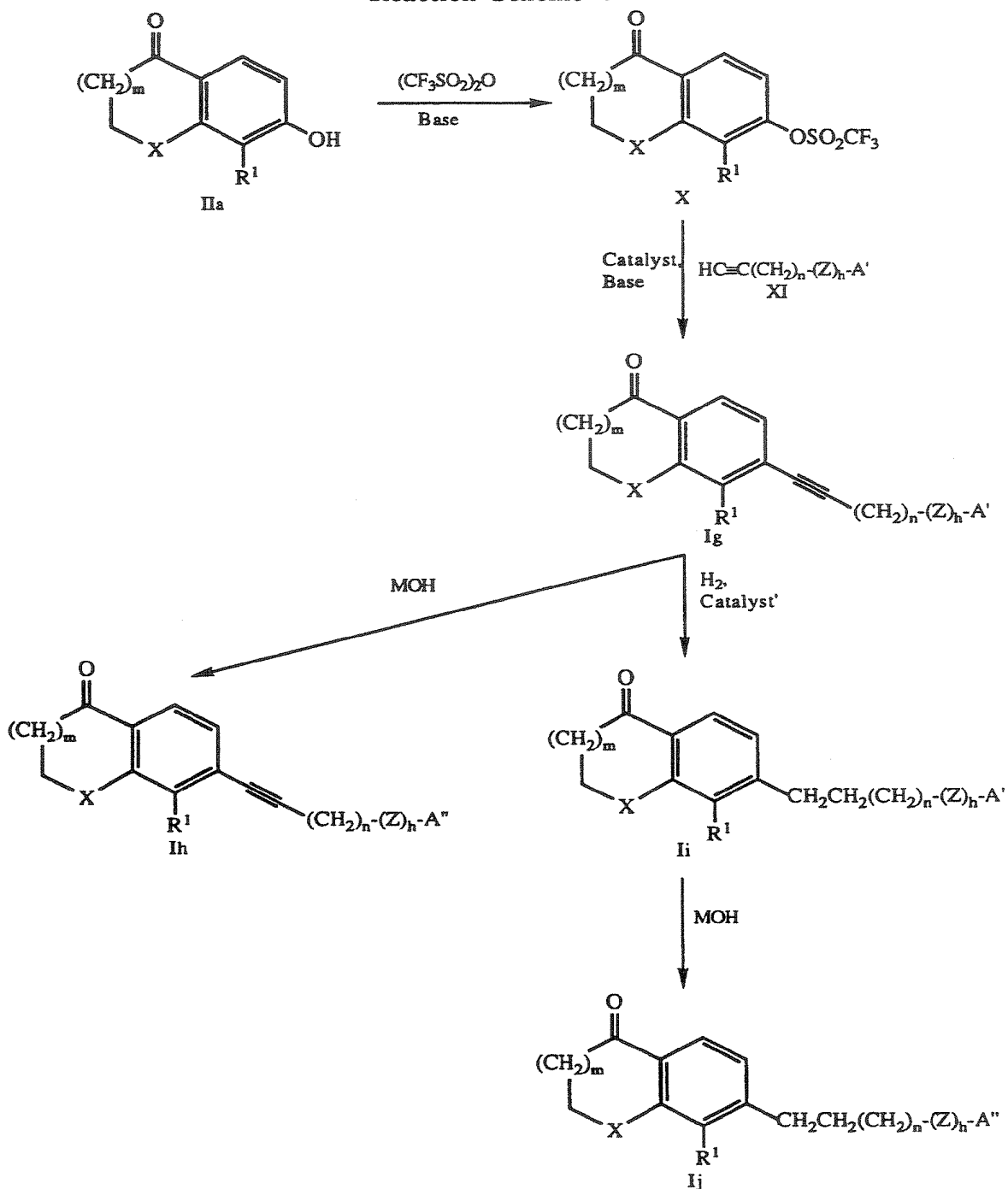


wherein  $\text{R}^5$  is lower alkyl and  $\text{R}^1$ , L, Z,  $\text{A}'$ ,  $\text{A}''$ , M, h and n are as previously described.

In Reaction Scheme 3, a dihydroxyacetophenone of formula VI which represents known compounds or compounds which can be prepared according to known procedures, is allowed to react with compound of formula III under conditions described in Reaction Scheme 1 for the conversion of II to Ia, giving a compound of formula VII. Treatment of a compound of formula VII with a known formamide acetal of formula VIII, at a temperature in the range of from 120° to 160°C, in an aromatic hydrocarbon solvent, preferably xylene, gives a compound which is not recovered but immediately cyclized by acid treatment to the chromone product of formula IX. Preferred acids for effecting this cyclization include the organic sulfonic acids such as para-toluenesulfonic acid. Preferred solvents for carrying out this cyclization include the lower alkanols such as methanol and ethanol, at a temperature in the range of 60° to 80°C. The resulting chromone of formula IX is generally recovered by conventional chromatographic methods. Catalytic hydrogenation of the chromone of formula IX gives the chromanone le. This hydrogenation is carried out under conventional conditions. A supported transition metal catalyst such as 5% or 10% palladium metal on carbon or charcoal is preferred. It is preferred that this hydrogenation be carried out at ambient temperature and under one atmosphere of hydrogen gas pressure. Preferred solvents for effecting this hydrogenation are the lower alkanols such as methanol or ethanol, or ester solvents such as ethyl acetate. Mixtures of these solvents can also be used. The resulting compound of formula le can be isolated

by conventional chromatographic means and saponified to the acid if using conditions described above for the saponification and recovery of esters Ia and Ic.

## Reaction Scheme 4



wherein X, R<sup>1</sup>, Z, A', A'', M, h, m and n are as previously described.

In Reaction Scheme 4, a compound of formula IIa is converted to the corresponding trifluoromethanesulfonate of formula X by treatment with trifluoromethanesulfonic anhydride in the presence of an amine base. Any conventional amine base may be utilized. Pyridine or triethylamine are preferred.



This transformation is preferably carried out in dichloromethane solvent at a temperature in the range of 0° to 25 °C. The compounds of formula X can be recovered by conventional means such as chromatography. The compound of formula X is allowed to react with an acetylenic compound of formula XI, which compound can be prepared according to known procedures or as hereinafter described (see, for example, Reaction Scheme 21, compounds LXXXVI and LXXXVIII), in the presence of a palladium catalyst and an amine base giving the compound of formula Ig. It is preferred that this transformation be carried out using dichlorobis(triphenylphosphine)palladium II as the catalyst and triethylamine as the base, in dimethylformamide solvent, at a temperature in the range of 80° to 100 °C. The product of formula Ig is recovered using conventional chromatographic techniques. Conventional catalytic hydrogenation of the compound of formula Ig, using conditions described in Scheme 5 gives the corresponding saturated compound of formula li. Saponification of the compound of formula li using conditions described in Reaction Scheme 1 gives the corresponding acid of formula lj. Alternatively, the compound of formula Ig can be directly saponified using the conditions described in Reaction Scheme 1 to give the corresponding acetylenic acid of formula lh. The compounds of formulas lh, li, and lj can be recovered by conventional chromatographic techniques or by conventional recrystallization.

20

25

30

35

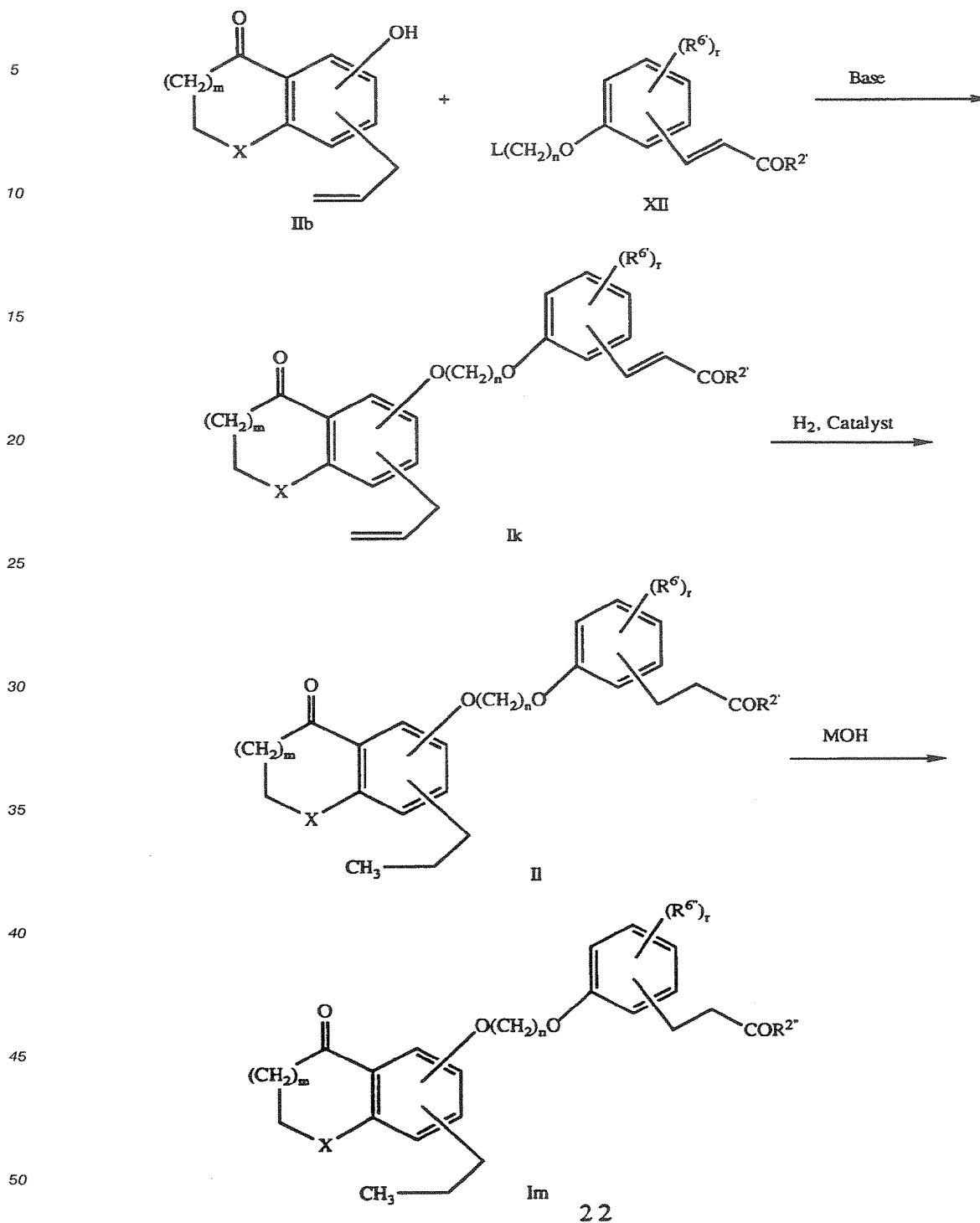
40

45

50

55

## Reaction Scheme 5



wherein  $r$  is an integer from 0 to 4,  $\text{R}^6$ , each occurrence, independently, is halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(\text{Q})_k-(\text{W})_s-\text{E}'$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}'$ , provided that no more than one of  $\text{R}^6$  is  $-(\text{Q})_k-(\text{W})_s-\text{E}'$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}'$ , and wherein  $\text{R}^{6'}$ , independently, is halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(\text{Q})_k-(\text{W})_s-\text{E}''$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}''$ , and provided that no more

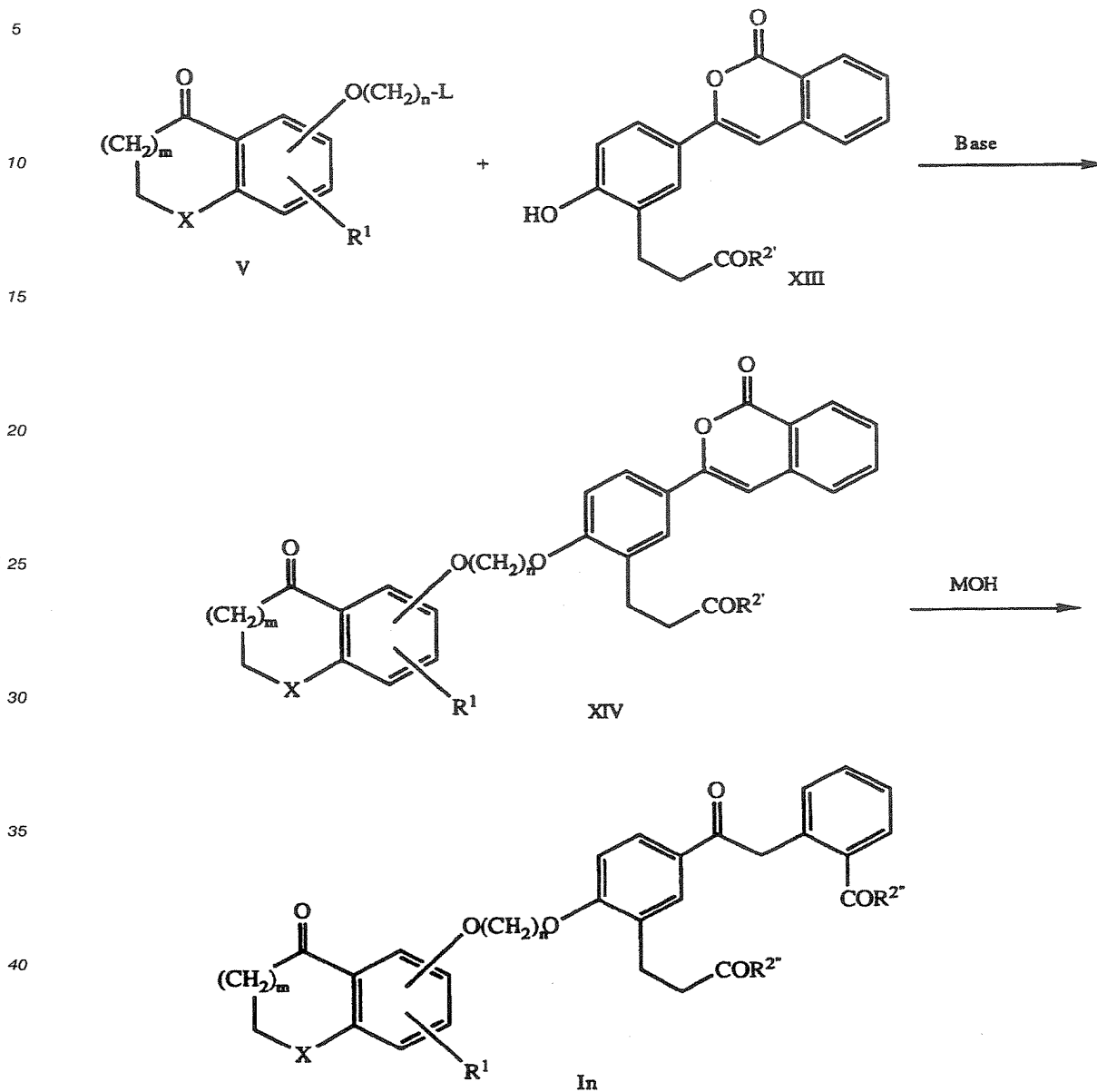
than one of  $R^{6''}$  is  $-(Q)_k-(W)_s-E''$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_s-E''$ , and wherein X, L,  $R^{2'}$ , Q, W,  $C_6H_4$ , M, m, n,  $s'$ ,  $s''$  and  $s'''$  are as previously described

In Reaction Scheme 5, a compound of formula IIb is allowed to react with a compound of formula XII which represents compounds which can be prepared as hereinafter described in Reaction Scheme 13, in the presence of a base, for example, an alkali metal carbonate, such as, sodium or potassium carbonate, at a temperature in the range of from about 25° to about 110°C, in a polar, aprotic solvent such as acetonitrile, N,N-dimethylformamide, 2-butanone, dimethyl sulfoxide or the like. Alternatively, the procedure of U.S. Patent No. 4,931,574 can be utilized. In this variation, a compound of formula IIb and one of formula XII are allowed to react in the presence of an alkali metal carbonate, preferably potassium carbonate, and a phase transfer catalyst, preferably tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1), in an aromatic hydrocarbon solvent, preferably toluene, at a temperature in the range of 80° to 110°C. The resulting compound of formula IIc can be recovered utilizing conventional methods, such as, chromatography or recrystallization.

Catalytic hydrogenation of the compound of formula IIc gives the corresponding saturated compound of formula II. The hydrogenation is carried out under conventional conditions. More specifically, a supported transition metal catalyst such as 5% or 10% palladium metal on carbon or charcoal is preferred. It is preferred that hydrogenation be carried out at ambient temperature and under one atmosphere of hydrogen gas pressure. Preferred solvents for the hydrogenation are lower alkanols such as methanol or ethanol, or ester solvents such as ethyl acetate, or the like. Mixtures of these solvents can also be used. The resulting compound of formula II can be isolated by conventional chromatographic means or the like.

The compound of formula II can be converted by saponification using an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, in a solvent mixture of water and a water miscible solvent such as methanol, ethanol or tetrahydrofuran, at a temperature in the range of from about 25° to about 60°C, to the corresponding acid of formula Im. The compounds of formula Im can be purified by conventional methods such as recrystallization or chromatography.

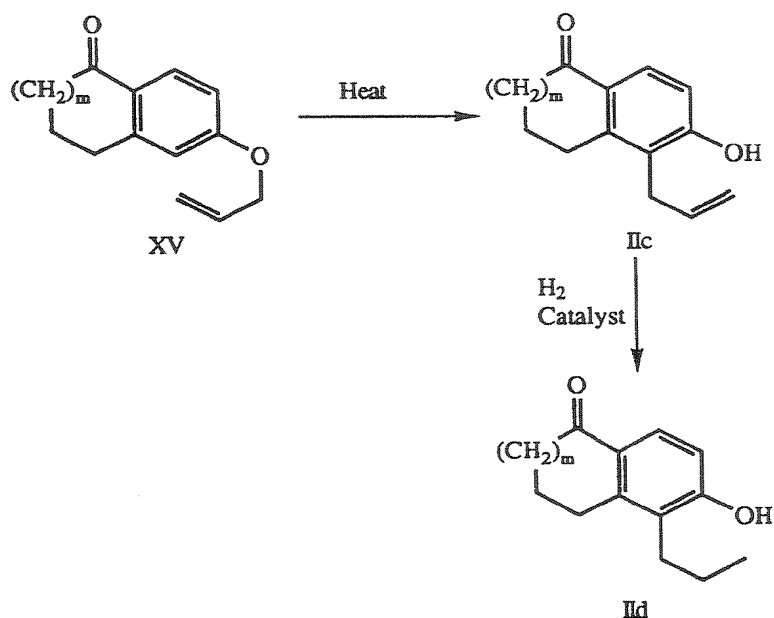
## Reaction Scheme 6



wherein R<sup>1</sup>, X, L, R<sup>2'</sup>, R<sup>2''</sup>, M, m and n are as previously described.

In Reaction Scheme 6, a compound of formula V is allowed to react with a compound of formula XIII, prepared as hereinafter described in Reaction Scheme 20, in the presence of a base and using conditions described in Scheme 1. The resulting compound of formula XIV is recovered using conventional recrystallization or chromatographic techniques. Saponification of the compound of formula XIV, using conditions as described in Reaction Scheme 1, gives the corresponding diacid of formula In which can be recovered, for example, by recrystallization.

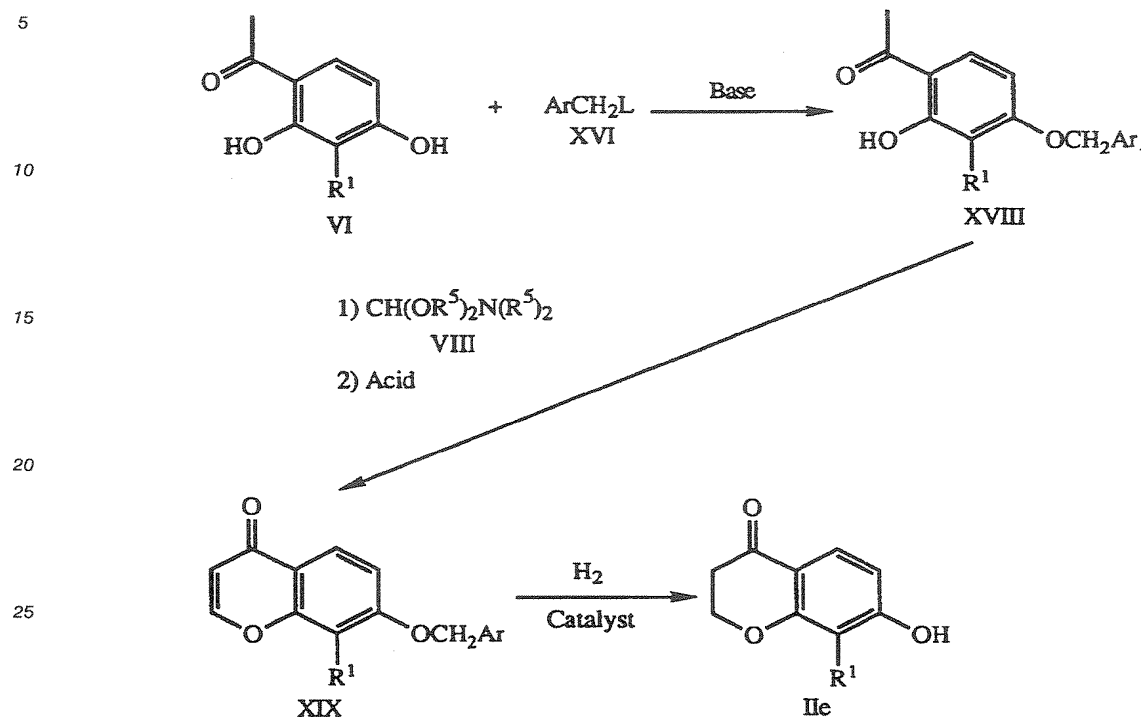
## Reaction Scheme 7



wherein m is as previously described.

In Reaction Scheme 7, an ether of formula XV, which represents known compounds, is thermolyzed in order to effect a Claisen rearrangement. It is preferred that the thermolysis be carried out at a temperature in the range of 180° to 195 °C and in the presence of a solvent of sufficiently high boiling point such as N,N-diethylaniline or without any solvent. The desired product of this thermolysis is the corresponding compound of formula IIc, which can be recovered by recrystallization. Catalytic hydrogenation of the resulting compound of formula IIc, using the standard conditions described in Reaction Scheme 5, gives the corresponding saturated compound of formula IId, which can be recovered by conventional chromatography, recrystallization or the like.

## Reaction Scheme 8

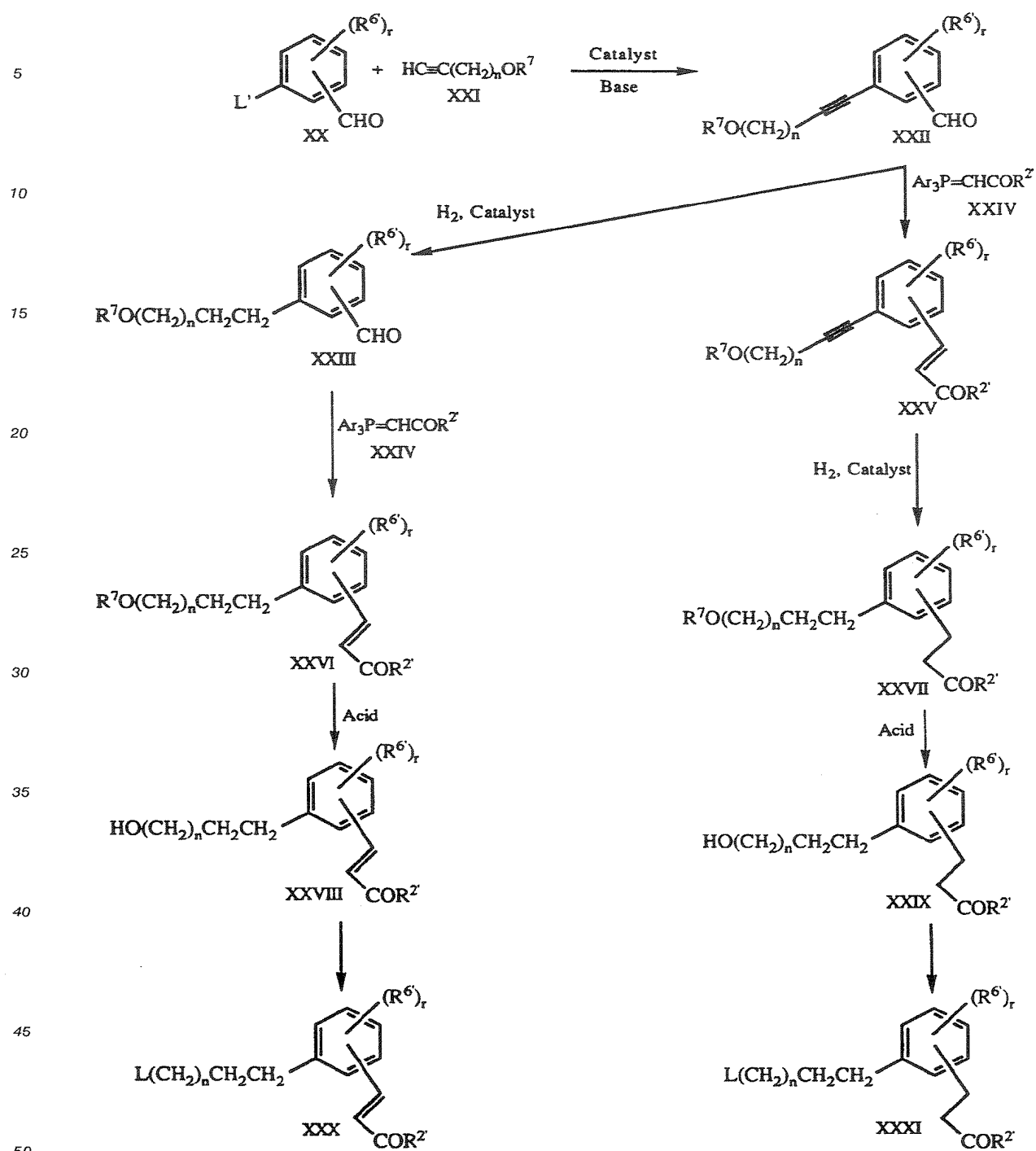


wherein Ar is aryl, R<sup>1</sup>, R<sup>5</sup> and L are as previously described.

In Reaction Scheme 8, a dihydroxyacetophenone of formula VI is allowed to react with a compound of formula XVI, which represents known compounds, under conditions described in Reaction Scheme 1 for the conversion of II to Ia, to give the corresponding compound of formula XVIII. Among the various compounds of formula XVI which can be employed, benzyl chloride or benzyl bromide are preferred. Treatment of the compound XVIII with a known formamide acetal of formula VIII followed by acidic cyclization, as described in Reaction Scheme 3 for the conversion of VII to IX, gives the corresponding chromone of formula XIX. The chromone of formula XIX is generally recovered by conventional chromatographic methods, recrystallization or the like.

Catalytic hydrogenation of the chromone XIX, with concomitant hydrogenolytic cleavage of the aryl-methyl ether moiety, gives the corresponding chromanone of formula IIc. The hydrogenation hydrogenolysis is carried out utilizing conventional conditions. A supported transition metal catalyst such as 5% or 10% palladium metal on carbon or charcoal is preferred. It is preferred that the hydrogenation be carried out at ambient temperature and under one atmosphere of hydrogen gas pressure. Preferred solvents for effecting the hydrogenation-hydrogenolysis are the lower alkanols such as methanol or ethanol, or ester solvents such as ethyl acetate, or the like. Mixtures of such solvents can also be used. The chromanone of formula IIc can be recovered by conventional chromatographic means.

## Reaction Scheme 9



wherein  $R^2$ ,  $R^6$ , Ar, L, r and n are as previously described and  $R^7$  is an acid labile hydroxy protecting group such as tetrahydropyranyl, trityl, t-butyl or the like, and  $L'$  is bromine, iodine or (trifluoromethyl)-sulfonyloxy.

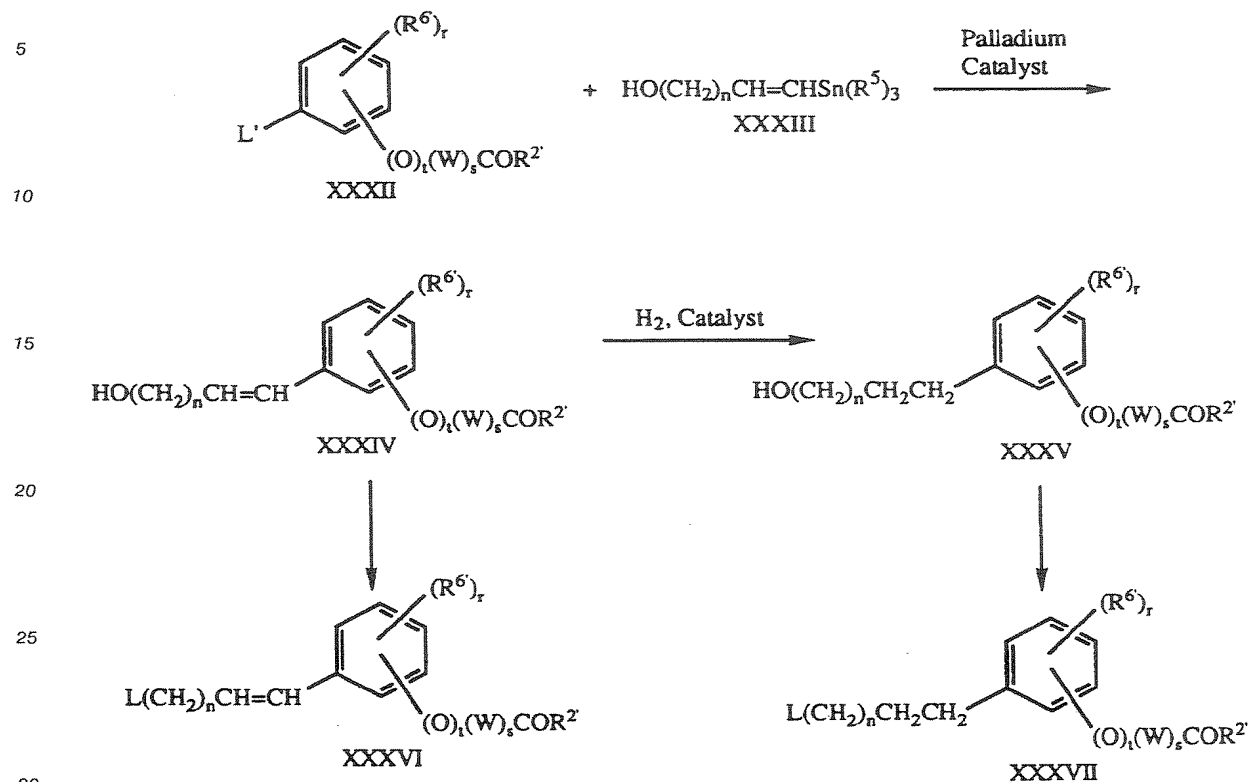
In Reaction Scheme 9, a benzaldehyde of formula XX, which represents known compounds or compounds which can be prepared according to known procedures or as hereinafter described, is allowed to react with an acetylene of formula XXI, which represents known compounds, in the presence of a palladium catalyst, a copper salt and an amine base to give the corresponding compound of formula XXII. A

preferred palladium catalyst is dichlorobis(triphenylphosphine)palladium II and a preferred copper salt is cuprous iodide. A preferred amine base is triethylamine which can also be used as the solvent medium. It is preferred that this reaction be carried out at a temperature in the range of 60° to 80 °C. The resulting compound of formula XXII is recovered by conventional chromatography or the like. Catalytic hydrogenation of the compound of formula XXII is carried out in the manner described in Reaction Scheme 4 for the conversion of Ig to li, to give the corresponding reduced compound of formula XXIII which is recovered conventionally. Condensation of the resulting aldehyde of formula XXIII with a phosphorane of formula XXIV, which represents compounds known in the art, gives the corresponding compound of formula XXVI. It is preferred that the condensation be carried out at a temperature in the range of 80° to 120 °C, in an aromatic hydrocarbon solvent. Toluene is a preferred solvent medium. The resulting compound of formula XXVI is recovered by chromatography or the like and is converted to the corresponding alcohol of formula XXVII by removal of the protecting group R<sup>7</sup> utilizing an acidic catalyst. It is preferred that the deprotection be carried out in a lower alkanol solvent such as methanol or ethanol. Useful acid catalysts for effecting the deprotection are organic sulfonic acids or amine salts thereof at a temperature in the range of 20° to 80° C. It is particularly preferred that the transformation be carried out using para-toluenesulfonic acid in methanol. The resulting compound of formula XXVIII is recovered by conventional chromatography or the like and is converted to the corresponding derivative of formula XXX using standard methods known in the art for transforming a hydroxy group into a leaving group L. These methods include treatment with halogenating reagents such as N-bromo-succinimide/triphenylphosphine or N-chlorosuccinimide/triphenylphosphine in dichloromethane. Alternatively, the compound of formula XXVIII can be converted to the corresponding sulfonate of formula XXX by conventional methods such as treatment with an alkyl- or arylsulfonyl chloride and an organic amine. It is preferred that the compound of formula XXVIII be treated with methanesulfonyl chloride and triethylamine in dichloromethane, ether or ethyl acetate at a temperature in the range of 0° to 25 °C.

Alternatively, an aldehyde of formula XXII can be converted to the corresponding compound of formula XXV by condensation with a compound of formula XXIV, as described for the conversion of XXIII to XXVI. Catalytic hydrogenation of the resulting compound of formula XXV as described for the conversion of XXII to XXIII gives the corresponding saturated compound of formula XXVII. The resulting compound of formula XXVII is converted to the corresponding alcohol of formula XXIX as described for the conversion of XXVI to XXVIII. The resulting compound of formula XXIX is converted to the corresponding compound of formula XXXI as described for XXVIII to XXX.



## Reaction Scheme 10

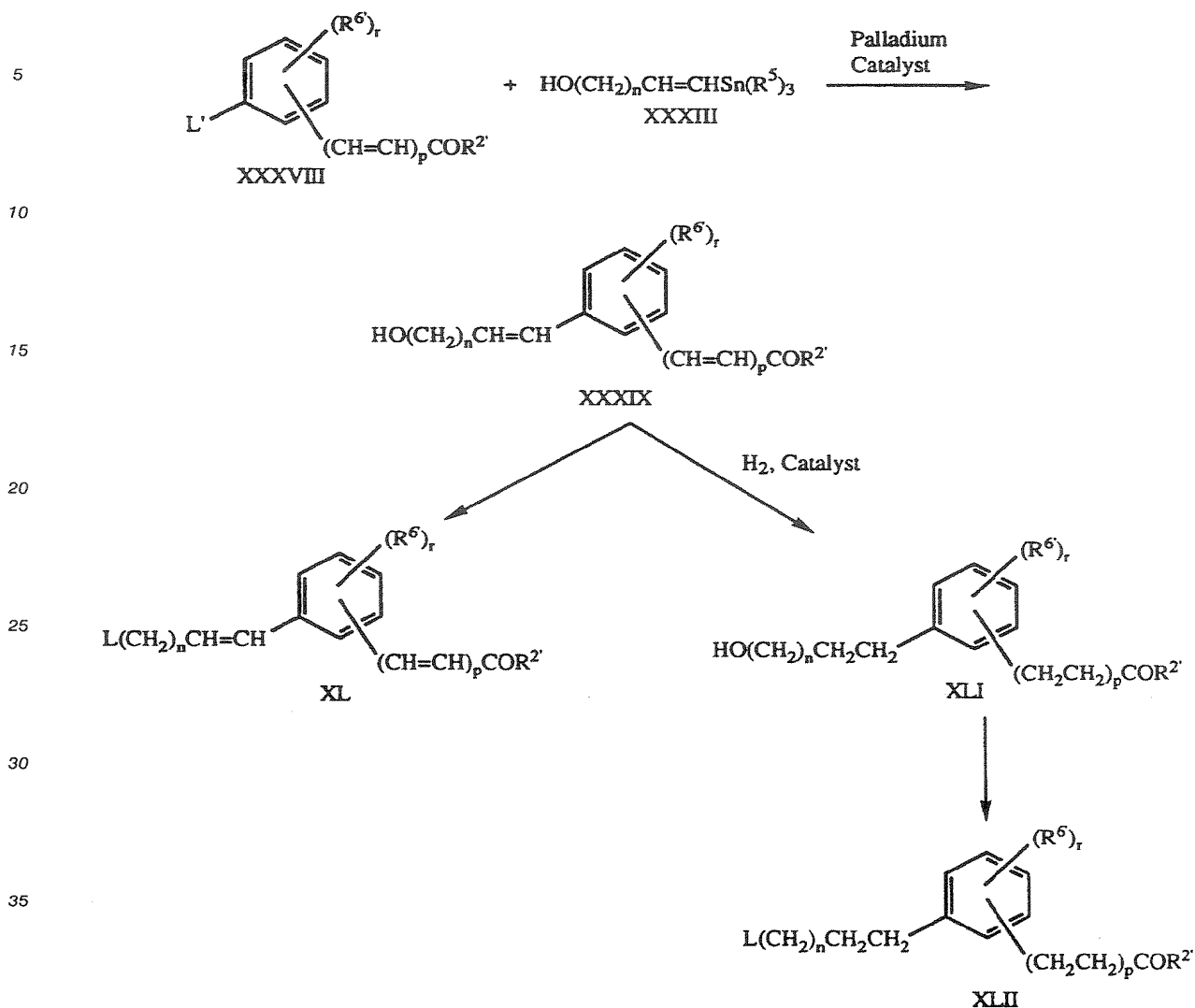


wherein  $\text{R}^5$ ,  $\text{R}^2$ ,  $\text{R}^6$ ,  $\text{L}$ ,  $\text{L}'$ ,  $\text{W}$ ,  $n$ ,  $s$ ,  $r$  and  $t$  are as previously described.

In Reaction Scheme 10, a compound of the formula XXXII, which represents known compounds or compounds which can be prepared according to known procedures or as hereinafter described, is allowed to react with an alkenylstannane of formula XXXIII, which represents known compounds, in the presence of a palladium catalyst to give the corresponding compound of formula XXXIV. The preferred palladium catalyst for effecting this transformation is a zero-valent palladium species such as tetrakis-(triphenylphosphine)palladium. The transformation is preferably carried out in the presence of an alkali metal halide salt such as lithium chloride and in an inert ether solvent, preferably dioxane. It is preferred that this reaction be carried out at a temperature in the range of 80° to 120 °C. The resulting compound of formula XXXIV is recovered by standard chromatographic techniques or the like. Catalytic hydrogenation of the compound of formula XXXIV under standard conditions described previously leads to the corresponding saturated compound of formula XXXV.

The compound of formula XXXV is recovered by conventional chromatography or the like and is converted to the corresponding derivative XXXVII using standard methods known in the art for transforming a hydroxy group into a leaving group, as described in Reaction Scheme 9 for the conversion of XXVIII to XXX. In a similar manner, the compound of formula XXXIV can be converted to the corresponding compound of formula XXXVI. Compounds XXXVI and XXXVII are recovered by standard chromatographic methods.

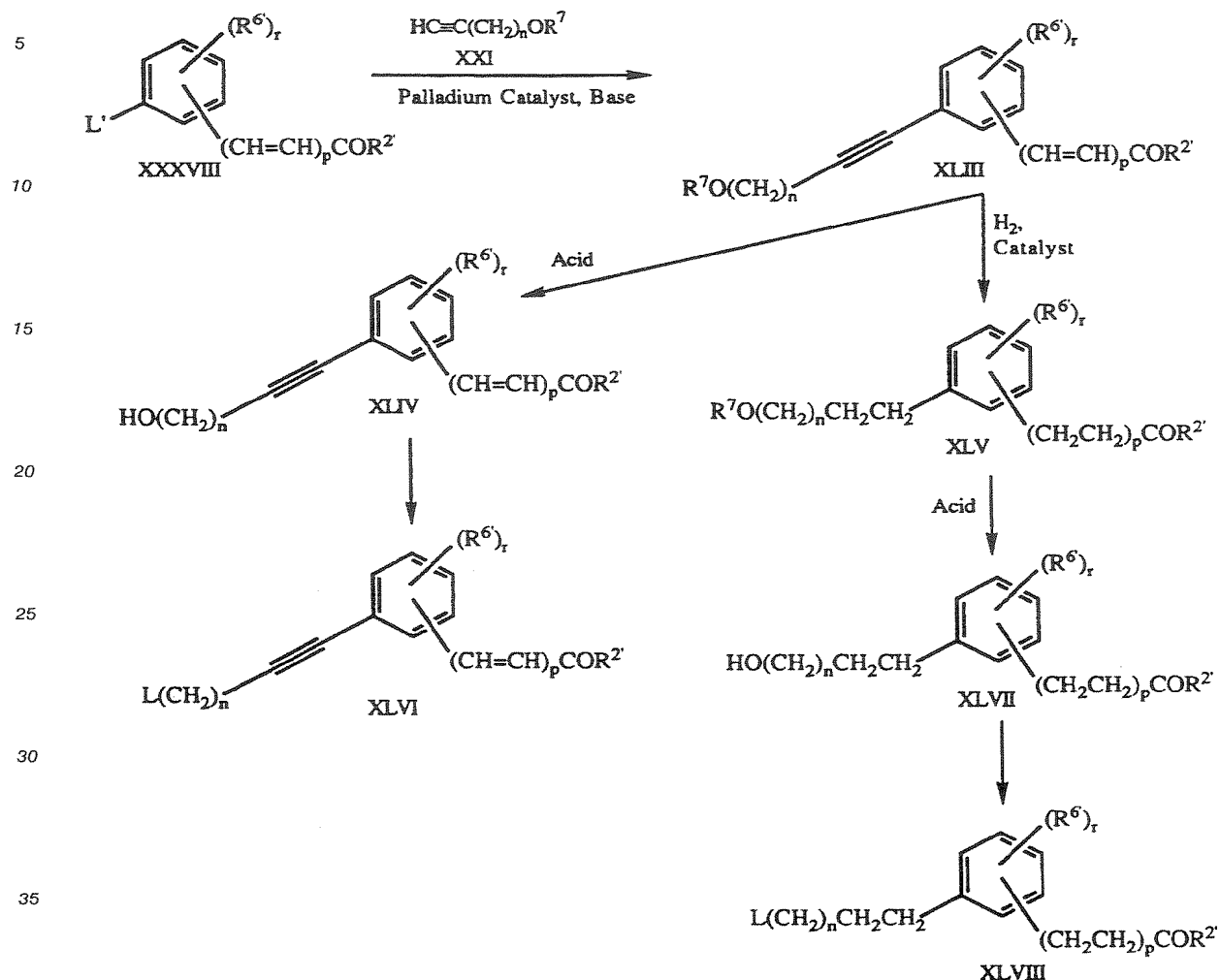
## Reaction Scheme 11



wherein  $R^2$ ,  $R^5$ ,  $R^6$ ,  $L$ ,  $L'$ ,  $n$ ,  $p$  and  $r$  are as previously described.

In Reaction Scheme 11, a compound of formula XXXVIII, which represents known compounds or compounds which can be prepared according to known procedures, is allowed to react with an alkenylstannane of the formula XXXIII in the presence of a palladium catalyst, to give the corresponding compound of formula XXXIX. The preferred palladium catalyst for effecting this transformation is a zero-valent palladium species such as tetrakis(triphenylphosphine) palladium. The transformation is preferably carried out in the presence of an alkali metal halide salt such as lithium chloride in an inert ether solvent, preferably dioxane. It is preferred that this reaction be carried out at a temperature in the range of  $80^\circ$  to  $120^\circ$  C. The compound of formula XXXIX is recovered by standard chromatographic techniques or the like. Catalytic hydrogenation of the compound of formula XXXIX under standard conditions described previously leads to the corresponding saturated compound of formula XLI. The compound of formula XLI is recovered by conventional chromatography or the like and is converted to the corresponding derivative XLII using standard methods known in the art for transforming a hydroxy group into a leaving group, as described in Reaction Scheme 9 for the conversion of a compound of formula XXVIII to a compound of formula XXX. In a similar manner, the compound of formula XXXIX is converted to the corresponding compound of formula XL. Compounds XL and XLII are recovered by standard chromatographic methods.

## Reaction Scheme 12

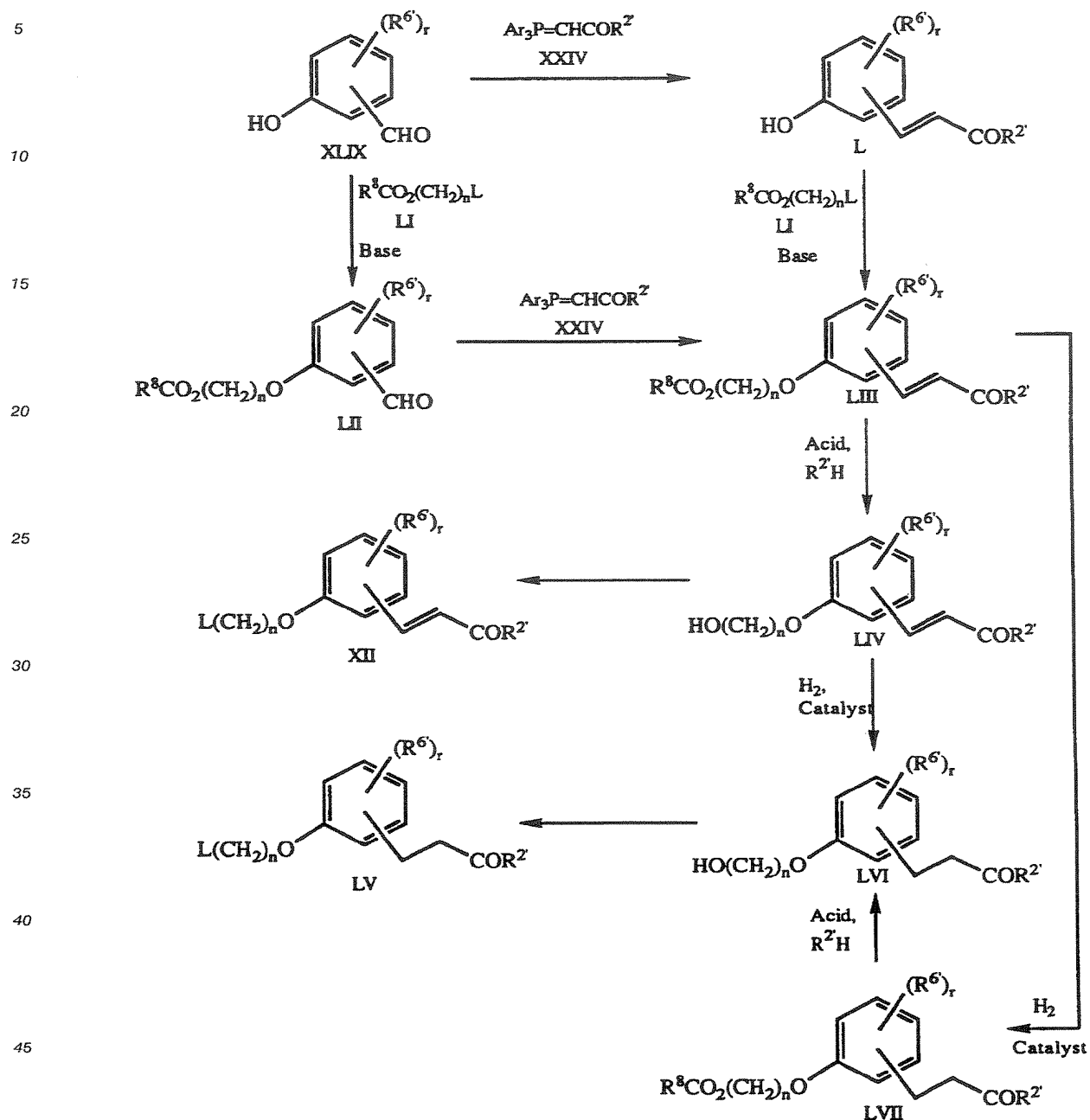


wherein  $R^2$ ,  $R^6$ ,  $R^7$ ,  $L$ ,  $L'$ ,  $n$ ,  $p$  and  $r$  are as previously described.

In Reaction Scheme 12, a compound of the formula XXXVIII is allowed to react with an acetylene of formula XXI in the presence of a palladium catalyst, a copper salt and an amine base to give the corresponding compound of formula XLIII using conditions described in Reaction Schemes 4 and 9 for the conversion of XX to XXII or for the conversion of X to Ig. The resulting compound of formula XLIII is recovered by conventional chromatography or the like. Catalytic hydrogenation of the compound of formula XLIII is carried out in the manner described in Reaction Scheme 4 for the conversion of Ig to li giving the corresponding reduced compound of formula XLV which is recovered conventionally. The compound of formula XLV is converted to the corresponding alcohol of formula XLVII by removal of the protecting group  $R^7$  utilizing an acidic catalyst as described in Reaction Scheme 9 for the conversion of XXVI to XXVIII. The compound of formula XLVII is recovered by conventional chromatography or the like and is converted to the corresponding derivative of formula XLVIII using standard methods known in the art for transforming a hydroxy group into a leaving group as described in Reaction Scheme 9 for the conversion of XXVIII to XXX.

Alternatively, the compound of formula XLIII can be converted to the compound of formula XLIV as described for the conversion of XXVI to XXVIII. The compound of formula XLIV is converted to the compound of formula XLVI as described for the conversion of XXVIII to XXX.

## Reaction Scheme 13



wherein  $R^8$  is hydrogen, lower alkyl or aryl and  $R^2$ ,  $R^6$ , L, Ar, n and r are as previously described.

In Reaction Scheme 13, a hydroxybenzaldehyde of the formula XLIX, which represents known compounds or compounds which can be prepared according to known procedures or as hereinafter described, is allowed to react with a phosphorane of formula XXIV, using the procedure and conditions described in Reaction Scheme 9 for the conversion of XXIII to XXVI, giving the corresponding compound L. The resulting compound of formula L is recovered by conventional chromatography or the like. Alkylation of the compound of formula L with an ester of formula LI, which represents known compounds, in the presence of a base gives the corresponding compound of formula LIII. The alkylation is carried out under standard conditions for effecting the alkylation of a phenol such as those described in Reaction Scheme 1

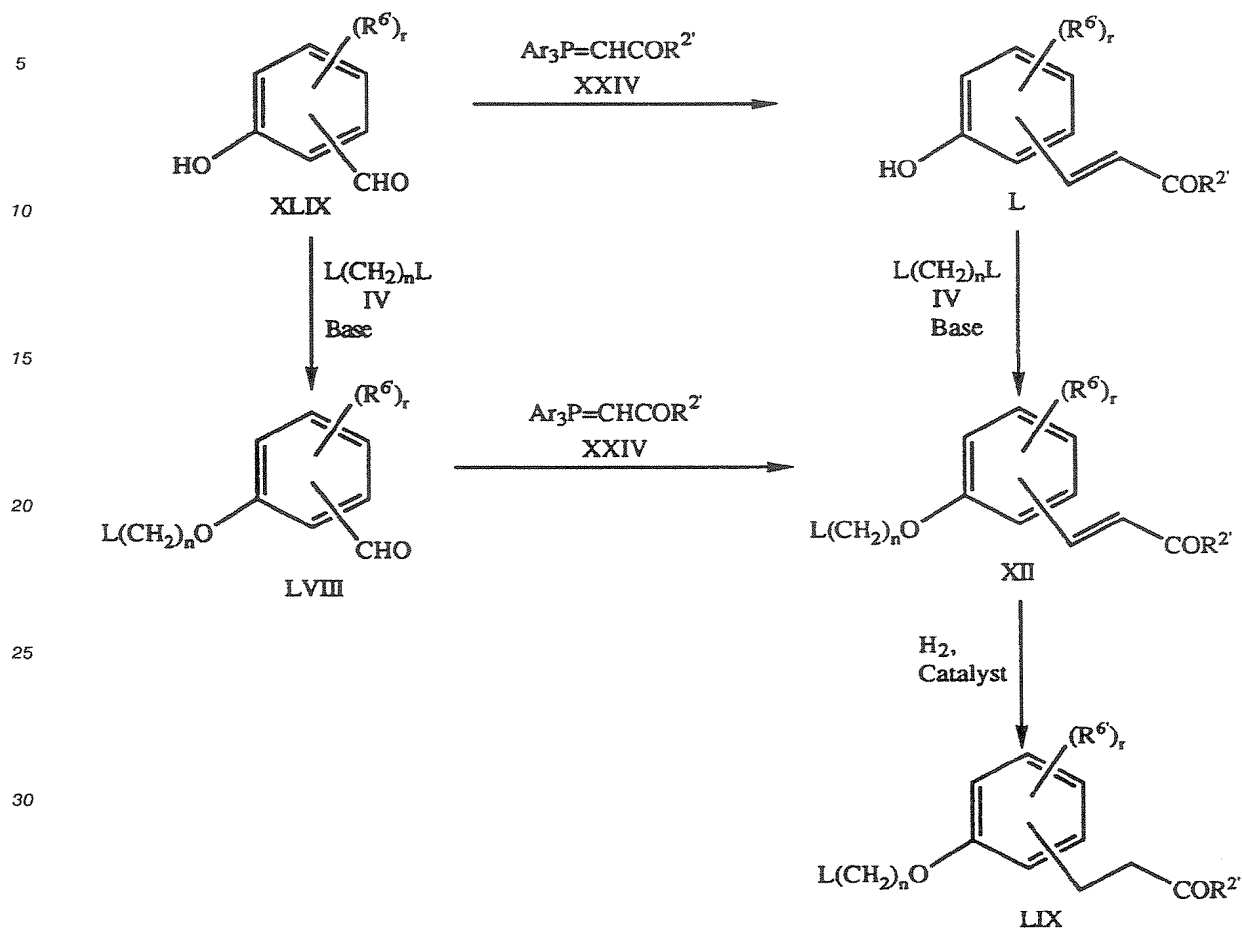
for the conversion of II to Ia. The compound of formula LIII is recovered by conventional chromatographic methods or the like. Alternatively, a compound of formula LIII can be prepared from the corresponding compound of formula XLIX by reversing this order of reactions, in other words, by first conventionally alkylating the compound of formula XLIX with the compound of formula LI to give the compound of formula LII. The compound of formula LII is then condensed with a phosphorane of formula XXIV to give the corresponding compound of formula LIII. The conditions required for effecting these transformations are as previously described.

A compound of formula LIII is converted to the corresponding alcohol of formula LIV by removal of the ester protecting group ( $R^8CO$ ) utilizing an acidic catalyst. It is preferred that the deprotection process be carried out by transesterification in a lower alkanol solvent which is  $R^2H$ . Useful acid catalysts for effecting the deprotection are organic sulfonic acids or amine salts thereof, at a temperature in the range of  $20^\circ$  to  $80^\circ C$ . It is particularly preferred that the transformation be carried out using para-toluenesulfonic acid in methanol. The resulting alcohol of formula LIV is recovered by conventional chromatography or the like and is converted to the corresponding derivative of formula XII using standard methods for transforming a hydroxy group into a leaving group such as those described in Reaction Scheme 9 for the conversion of XXVIII to XXX.

Alternatively, catalytic hydrogenation of a compound of formula LIV gives the corresponding saturated compound of formula LVI as described in Reaction Scheme 9 for the conversion of XXV to XXVII. The resulting compound of formula LVI is converted to the corresponding compound of formula LV as described in Reaction Scheme 9 for the conversion of XXVIII to XXX.

In yet another variation, conventional catalytic hydrogenation of a compound of formula LIII gives the corresponding saturated derivative of formula LVII. The resulting compound of formula LVII is then converted to the corresponding compound of formula LVI as described for the conversion LIII to LIV.

## Reaction Scheme 14

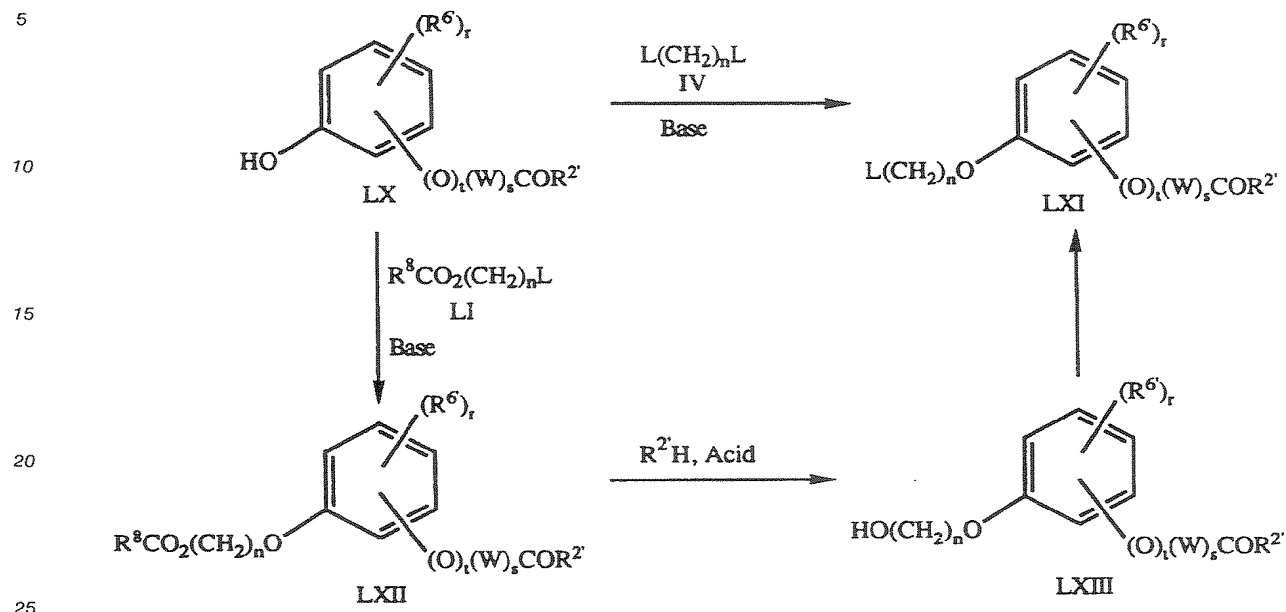


wherein  $R^{2'}$ ,  $R^6$ , L, Ar, n and r are as previously described.

In Reaction Scheme 14, a hydroxybenzaldehyde of formula XLIX, is alkylated with a compound of formula IV using the conditions described in Reaction Scheme 2 for the conversion of II to V. The resulting compound of formula LVIII is recovered by conventional chromatography or the like. The compound of formula LVIII is then condensed with a phosphorane of formula XXIV to give the corresponding compound of formula XII. The conditions required for effecting these transformations are as previously described.

Alternatively, a compound of formula L, prepared as described in Reaction Scheme 13, is alkylated with a compound of formula IV using the conditions described in Reaction Scheme 2 for the conversion of II to V to give the corresponding compound of formula XII. Catalytic hydrogenation of a compound of formula XII gives the corresponding saturated derivative of formula LIX. It is preferred that this hydrogenation be performed using a catalyst compatible with the preservation of the leaving group "L" in an inert solvent. Preferred conditions for effecting the reduction involve the use of rhodium on alumina as the catalyst and toluene as the solvent under one atmosphere of hydrogen pressure at a temperature in the range of  $0^\circ$  to  $25^\circ$  C.

## Reaction Scheme 15

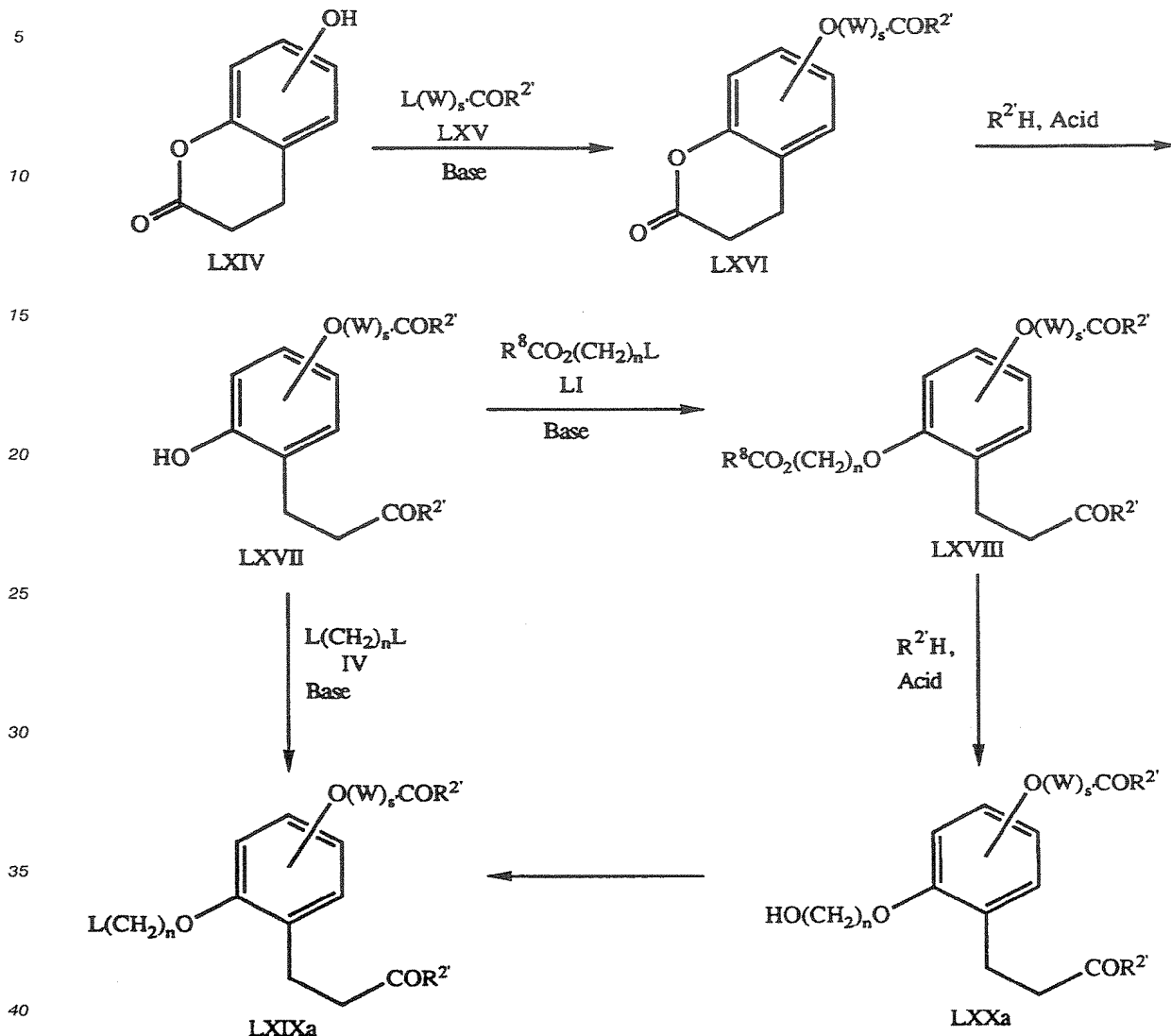


wherein  $\text{R}^2'$ ,  $\text{R}^6$ ,  $\text{R}^8$ ,  $\text{L}$ ,  $\text{W}$ ,  $n$ ,  $s$ ,  $r$  and  $t$  are as previously described.

Alkylation of a phenol of formula LX, which represents known compounds or compounds which can be prepared according to known procedures or as hereinafter described, with an ester of formula LI in the presence of a base, gives the corresponding compound of formula LXII. This alkylation is carried out under standard conditions for effecting the alkylation of a phenol such as those described in Reaction Scheme 1 for the conversion II to Ia. The resulting compound of formula LXII is recovered by conventional chromatographic methods or the like. A compound of formula LXII is converted to the corresponding alcohol of formula LXIII by removal of the ester protecting group ( $\text{R}^8\text{CO}$ ) using an acidic catalyst. The transformation is carried out as described in Reaction Scheme 13 for the conversion of LIII to LIV. The compound of formula LXIII can be recovered by conventional chromatography or the like and is converted to the corresponding derivative LXI using standard methods for transforming a hydroxy group into a leaving group such as those described in Reaction Scheme 9 for the conversion of XXVIII to XXX.

Alternatively, a phenol of formula LX can be alkylated with a compound of formula IV to give the corresponding compound of formula LXI. The alkylation is carried out under conditions described in Reaction Scheme 2 for the conversion of II to V.

## Reaction Scheme 16



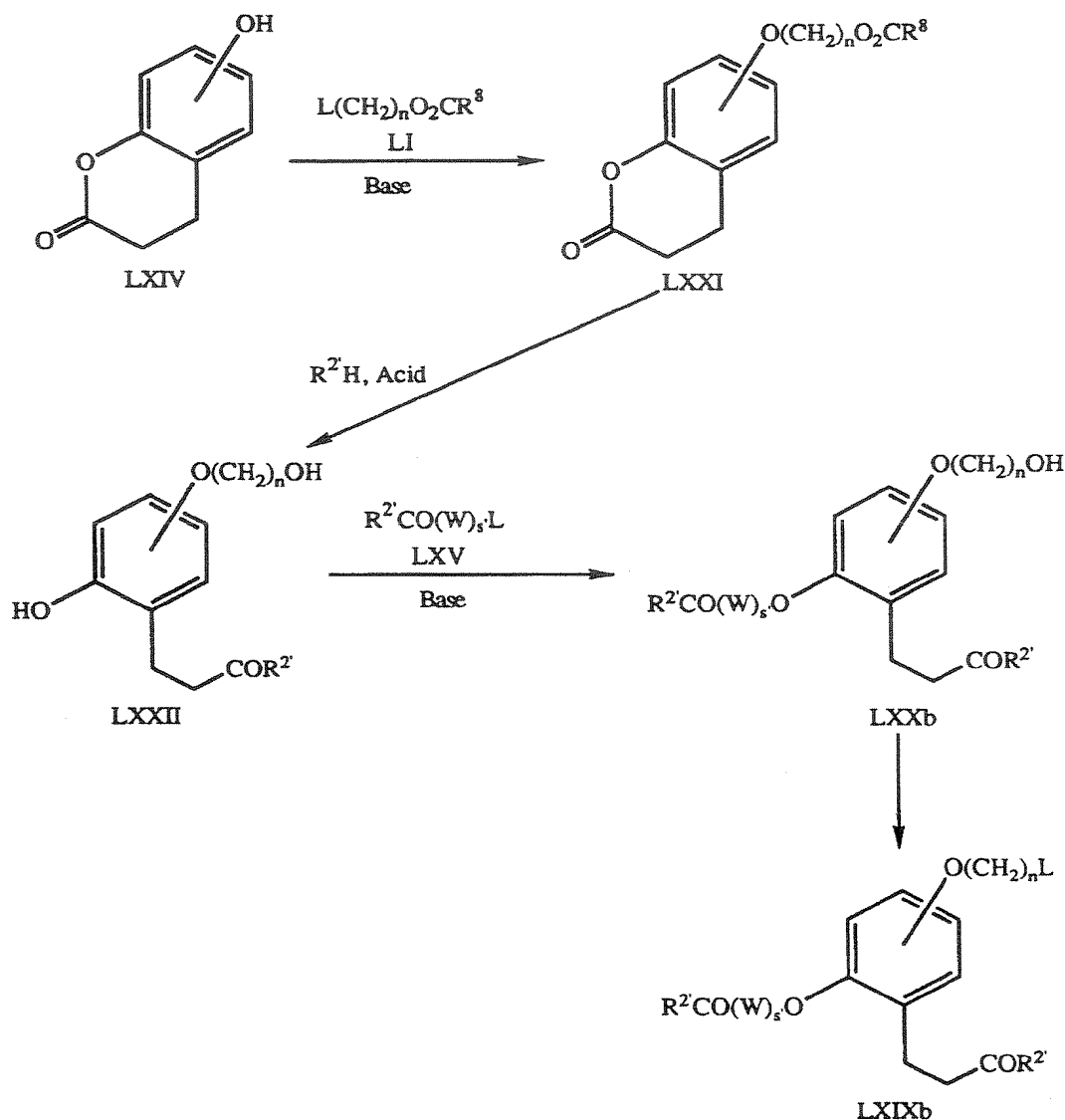
wherein  $R^2$ ,  $R^8$ , L, W, n and s' are as previously described.

In Reaction Scheme 16, alkylation of a dihydrocoumarin of formula LXIV, which represents known compounds, with an ester of formula LXV, which also represents known compounds, in the presence of a base gives the corresponding compound of formula LXVI. The alkylation can be carried out under standard conditions for effecting the alkylation of a phenol such as those described in Reaction Scheme 13 for the conversion of L to LIII. The resulting compound of formula LXVI can be recovered by conventional chromatographic methods. The compound of formula LXVI is converted to the corresponding phenol of formula LXVII by alcoholysis of the lactone ring using an acidic catalyst in a lower alcohol solvent. The transformation is carried out using any of the common acids, such as, hydrochloric or sulfuric acid, an alkyl sulfonic acid or an arylsulfonic acids. It is preferred that this transformation be carried out in methanol or ethanol with para-toluenesulfonic acid at a temperature in the range of 60° to 80 °C. The compound of formula LXVII can be recovered by standard chromatographic methods or the like. Alkylation of the compound of formula LXVII with a compound of formula IV is carried out as described in Reaction Scheme 2 for the conversion of II to V and affords the corresponding compound of formula LXIXa, which is recovered by chromatography.



Alternatively, a compound of formula LXVII is alkylated with a compound of formula LI to give the corresponding compound of formula LXVIII. This alkylation is carried out as described in Reaction Scheme 13 for the conversion of L to LIII. The compound of formula LXVIII which is recovered by conventional chromatography or the like is converted to the corresponding alcohol of formula LXXa as described in Reaction Scheme 13 for the conversion of LIII to LIV. The compound of formula LXXa is recovered by chromatography or the like and is converted to the compound of formula LXIXa using procedures described in Reaction Scheme 9 for the conversion of XVIII to XXX.

### Reaction Scheme 17

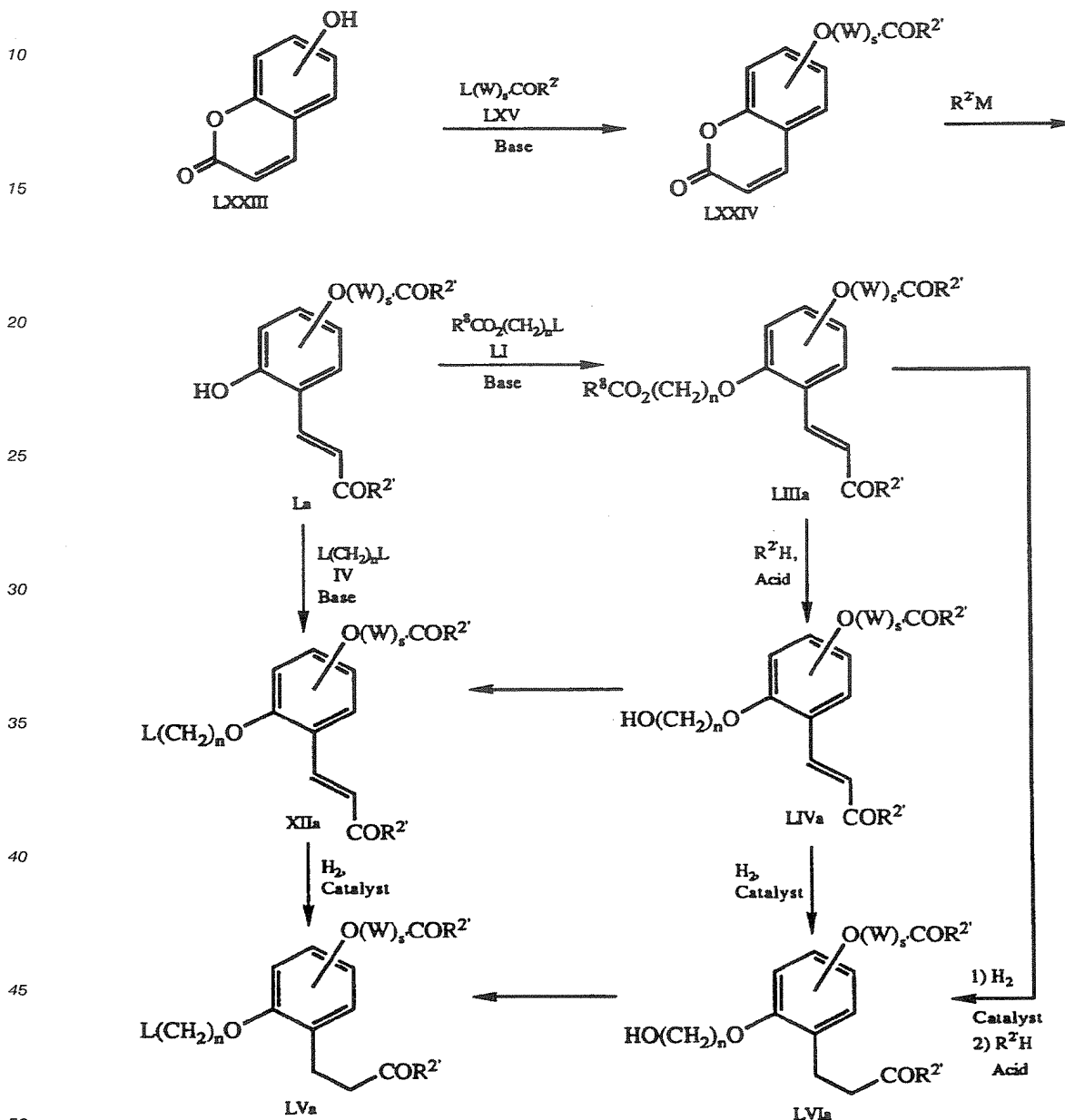


wherein  $R^{2'}$ ,  $R^8$ ,  $Z$ ,  $L$ ,  $W$ ,  $n$  and  $s'$  are as previously described.

In Reaction Scheme 17, alkylation of the dihydrocoumarin of formula LXIV with an ester of formula LI, as described in Reaction Scheme 13 for the conversion of L to LIII, gives the corresponding compound of formula LXXI. The resulting compound of formula LXXI is converted to the corresponding phenol of formula LXXII as described in Reaction Scheme 16 for the conversion of LXVI to LXVII. The compound of formula LXXII is recovered by standard chromatographic methods or the like. Alkylation of a compound of formula LXXII with a compound of formula LXV can be carried out as described in Reaction Scheme 16 for the

conversion of LXIV to LXVI, and gives the corresponding compound of formula LXXb which can be recovered by chromatography or the like. A compound of formula LXXb can be converted to the corresponding compound of formula LXIXb using procedures described in Reaction Scheme 9 for the conversion of XXVIII to XXX.

## Reaction Scheme 18



wherein  $R^{2'}$ ,  $R^8$ ,  $L$ ,  $W$ ,  $M$ ,  $n$  and  $s'$  are as previously described.

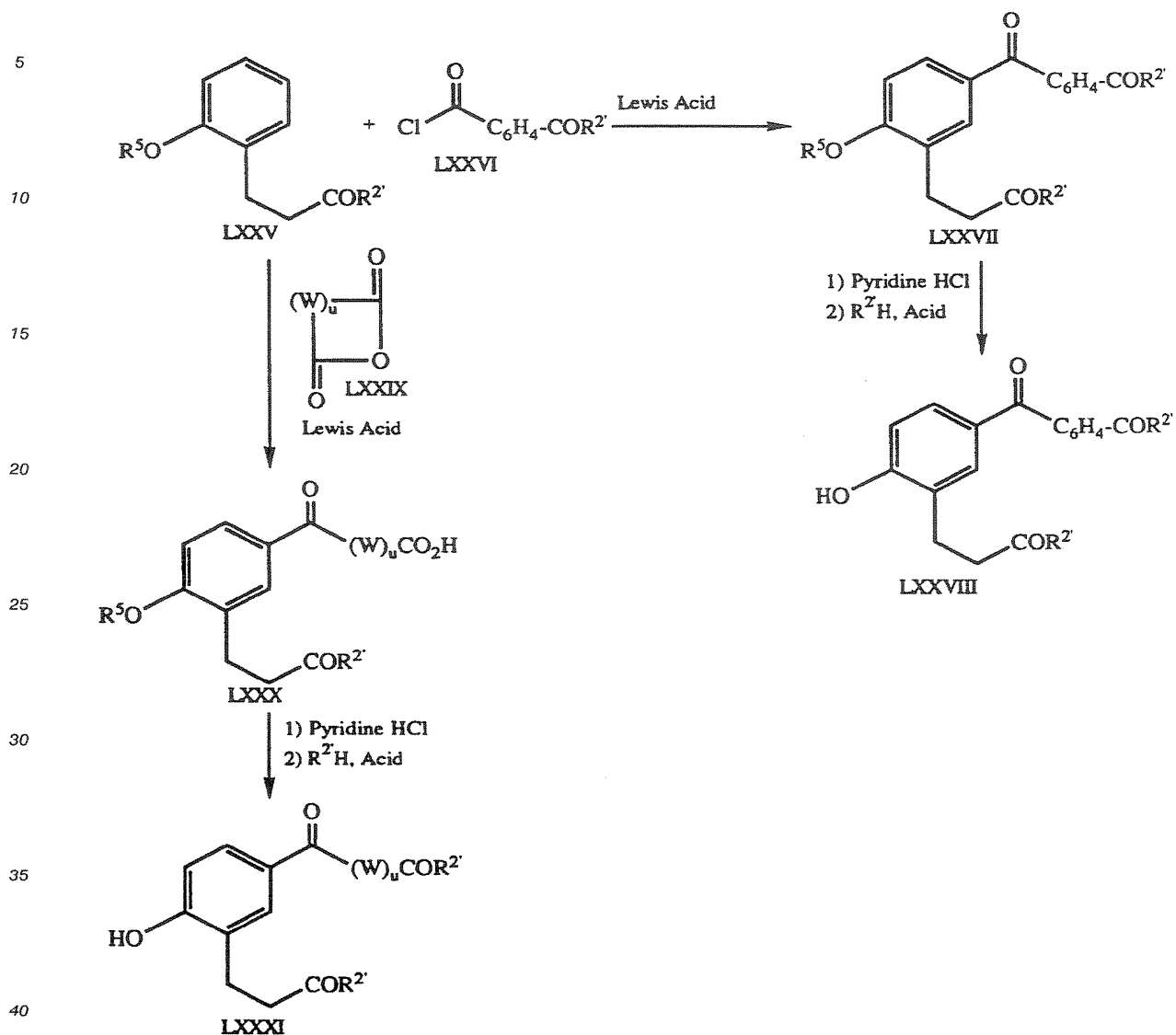
In Reaction Scheme 18, alkylation of a coumarin of formula LXXIII, which represents known compounds, with an ester of formula LXV in the presence of a base gives the corresponding compound of formula LXXIV. The alkylation is carried out under standard conditions for effecting the alkylation of a phenol such as those described in Reaction Scheme 13 for the conversion of L to LIII. The compound of formula LXXIV is recovered by conventional chromatographic methods or the like. A compound of formula LXXIV can be converted to the corresponding phenol of formula La by alcoholysis of the lactone ring using an alkali metal

lower alkoxide in a lower alkanol solvent. The transformation can be carried out using lithium, sodium or potassium lower alkoxide. It is preferred that the transformation be carried out in methanol or ethanol with sodium methoxide or sodium ethoxide, respectively, at a temperature in the range of 60° to 80 °C. The compound of formula La is recovered by standard chromatographic methods. Alkylation of a compound of formula La with a compound of formula IV is carried out as described in Reaction Scheme 2 for the conversion of II to V and gives the corresponding compound of formula XIIa which is recovered by chromatography. Catalytic hydrogenation of a compound of formula XIIa using the procedure described in Reaction Scheme 14 for the conversion XII to LIX gives the corresponding saturated compound of formula LVa.

Alternatively, a compound of formula La is alkylated with a compound of formula LI giving the corresponding compound of formula LIIIa. The alkylation is carried out as described in Reaction Scheme 13 for the conversion of L to LIII. A compound of formula LIIIa, which is recovered by conventional chromatography or the like, is converted to the corresponding alcohol of formula LIVa as described in Reaction Scheme 13 for the conversion of LIII to LIV. The compound of formula LIVa is recovered by chromatography and is converted to the corresponding compound of formula XIIa using procedures described in Reaction Scheme 9 for the conversion of XXVIII to XXX. Catalytic hydrogenation of a compound of formula LIVa gives the corresponding saturated compound LVIIa which, in turn, can be transformed to the corresponding compound of formula LVa using the standard methodology described previously.

If desired, a compound of formula LIIIa can be first hydrogenated and the ester protecting group removed as previously described to give the corresponding saturated alcohol of formula LVIIa. The resulting compound of formula LVIIa can then be converted to the corresponding compound of formula LVa. All of these transformations are carried out using the standard reaction and the recovery procedures previously described.

## Reaction Scheme 19



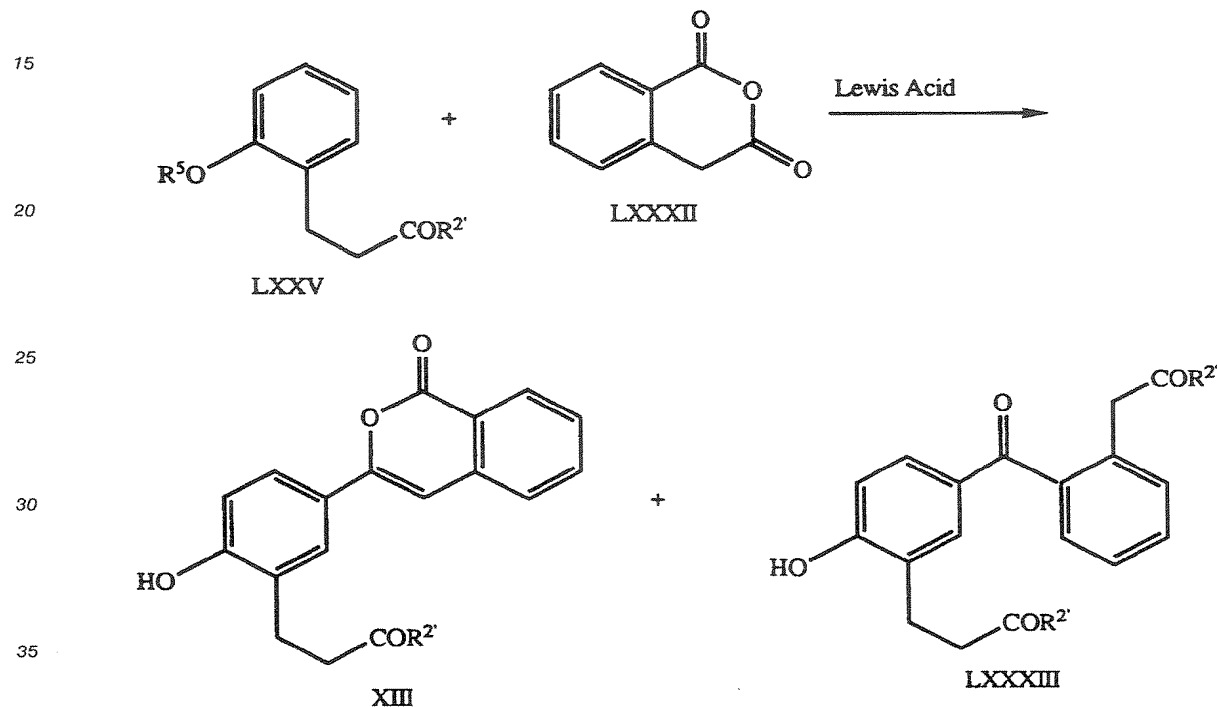
wherein  $R^{2'}$ ,  $R^5$ ,  $W$  and  $C_6H_4$  are as previously described and  $u$  is an integer of 2 or 3.

In Reaction Scheme 19, an ether ester of formula LXXV, which represents known compounds, is caused to undergo Friedel-Crafts acylation with an acid chloride ester of the formula LXXVI, which also represents known compounds, in the presence of a Lewis acid to give the corresponding keto diester compound of formula LXXVII. Any standard Lewis acid such as aluminum, boron or titanium halides can be employed in the reaction. The acylation can be carried out in an inert solvent such as a halogenated hydrocarbon or an aromatic hydrocarbon. It is preferred that the acylation be carried out using aluminum chloride in dichloromethane at a temperature in the range of  $25^\circ$  to  $120^\circ$  C. The compound of formula LXXVII can be recovered by chromatography or recrystallization. Removal of the lower alkyl ether protecting group  $R^5$  in a compound of formula LXXVII can be effected using any of the known method for dealkylation of alkyl aryl ethers, for example, by treatment with a mineral acid such as hydrogen bromide or hydrogen iodide and the like and amine salts thereof. Aluminum and boron halides can also be used. It is preferred that the dealkylation be carried out by heating a compound of formula LXXVII with pyridine hydrochloride at a temperature in the range of  $180^\circ$  to  $220^\circ$  C. Since this treatment also induces cleavage of the ester groups ( $R^{2'}$ ), the acid product of the dealkylation is immediately subjected to reesterification using standard Fischer esterification conditions which involve exposure of the crude reaction product to the lower alkanol of

the formula  $R^2H$  and a strong acid catalyst such as para-toluenesulfonic acid, hydrogen chloride or thionyl chloride. The resulting keto diester phenol product of formula LXXVIII is recovered by conventional chromatography or the like.

Friedel-Crafts acylation of a compound of formula LXXV with an anhydride of formula LXXIX, which represents known compounds is carried out as described for the conversion of LXXV to LXXVII, to give the corresponding ester acid compound of the formula LXXX. A compound of formula LXXX is dealkylated and reesterified as described for the conversion of LXXVII to LXXVIII to give the corresponding keto diester phenol compound of formula LXXXI which can be recovered by chromatography or the like.

### Reaction Scheme 20

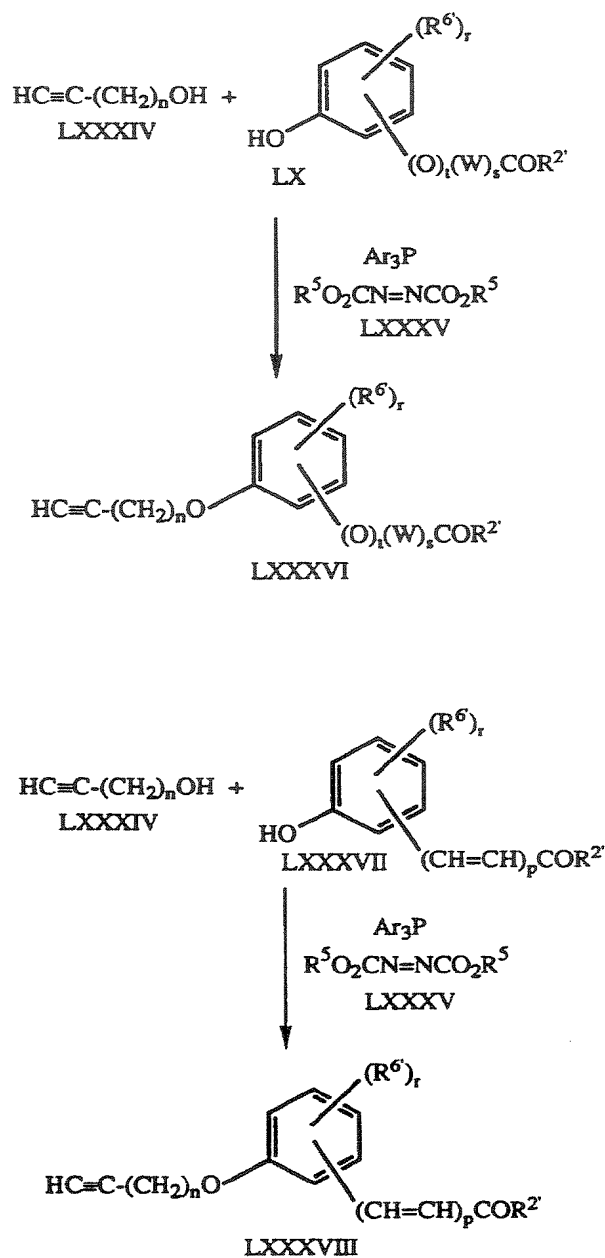


wherein  $R^2$  and  $R^5$  are as previously described.

In Reaction Scheme 20, an ether ester of formula LXXV is caused to undergo Friedel-Crafts acylation with the known homophthalic anhydride of the formula LXXXII, in the presence of a Lewis acid to give a mixture of compounds which can be separated by chromatography into ether and phenol functions. The separated ether products of the mixture are dealkylated and reesterified giving the corresponding compounds of formulae XIII and LXXXIII, which can be recovered by conventional chromatography or the like.

The procedures employed for carrying out the transformations are as described in Reaction Scheme 19 for the conversion of LXXV to LXXVIII.

## Reaction Scheme 21



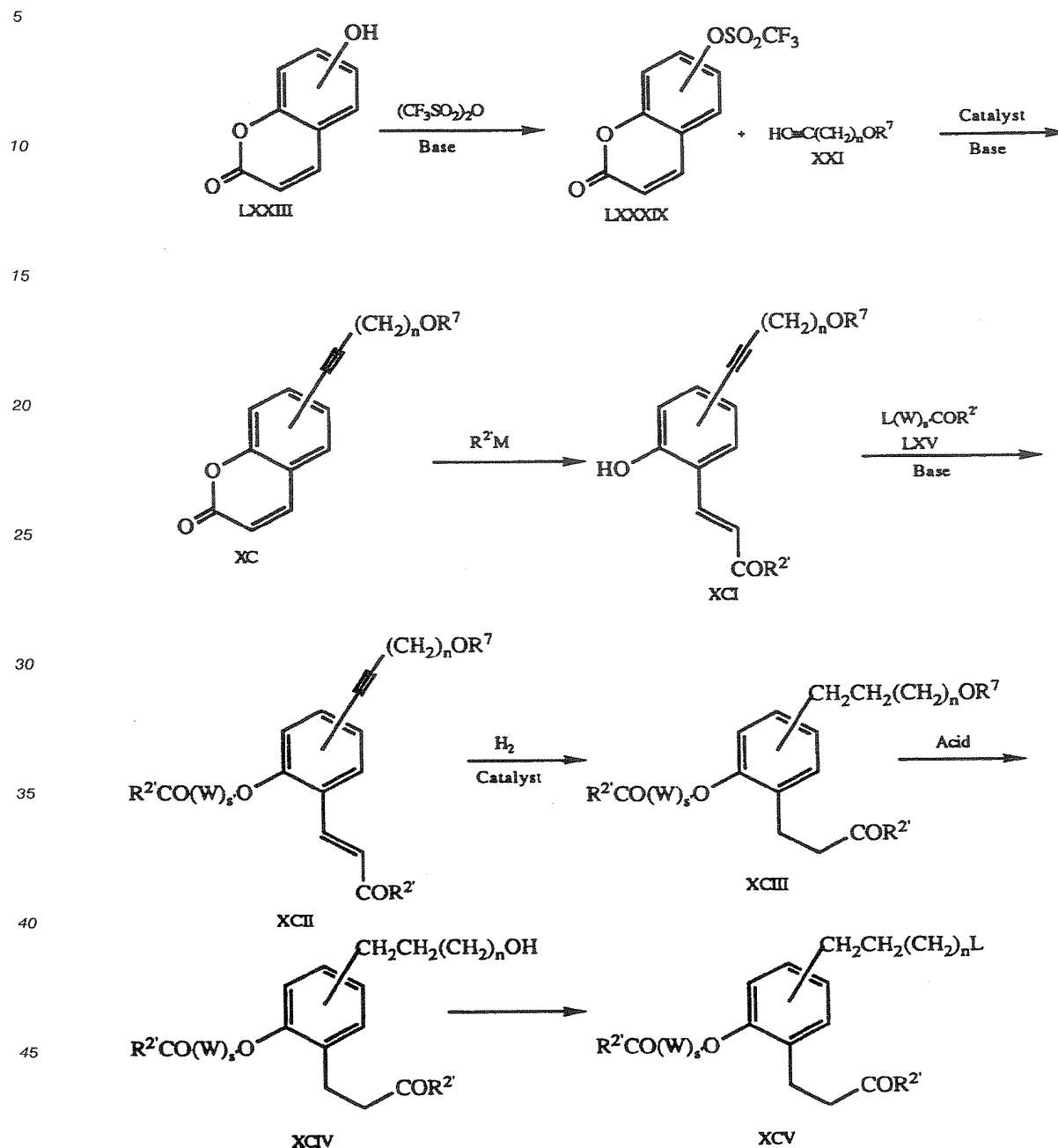
wherein  $\text{R}^{2'}$ ,  $\text{R}^5$ ,  $\text{R}^6$ , Ar, W, n, p, s, r and t are as previously described.

In Reaction Scheme 21, an alkynol of formula LXXXIV, which represents known compounds, is condensed with a phenol of formula LX to give the corresponding ether compound of formula LXXXVI. The condensation is carried out by treatment of the reactants with a triarylphosphine and a di-lower alkyl ester of azodicarboxylic acid of the formula LXXXV in an inert solvent. It is preferred that the condensation be carried out using triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran solution at a temperature in the range of 25° to 50 °C. The resulting product of formula LXXXVI can be recovered by chromatography or the like.

In a similar manner, the alkynol of formula LXXXIV is condensed with a phenol of formula LXXXVII, prepared as herein described (see, for example, Reaction Scheme 13, compound L), to give the cor-

responding compound of formula LXXXVIII.

## Reaction Scheme 22

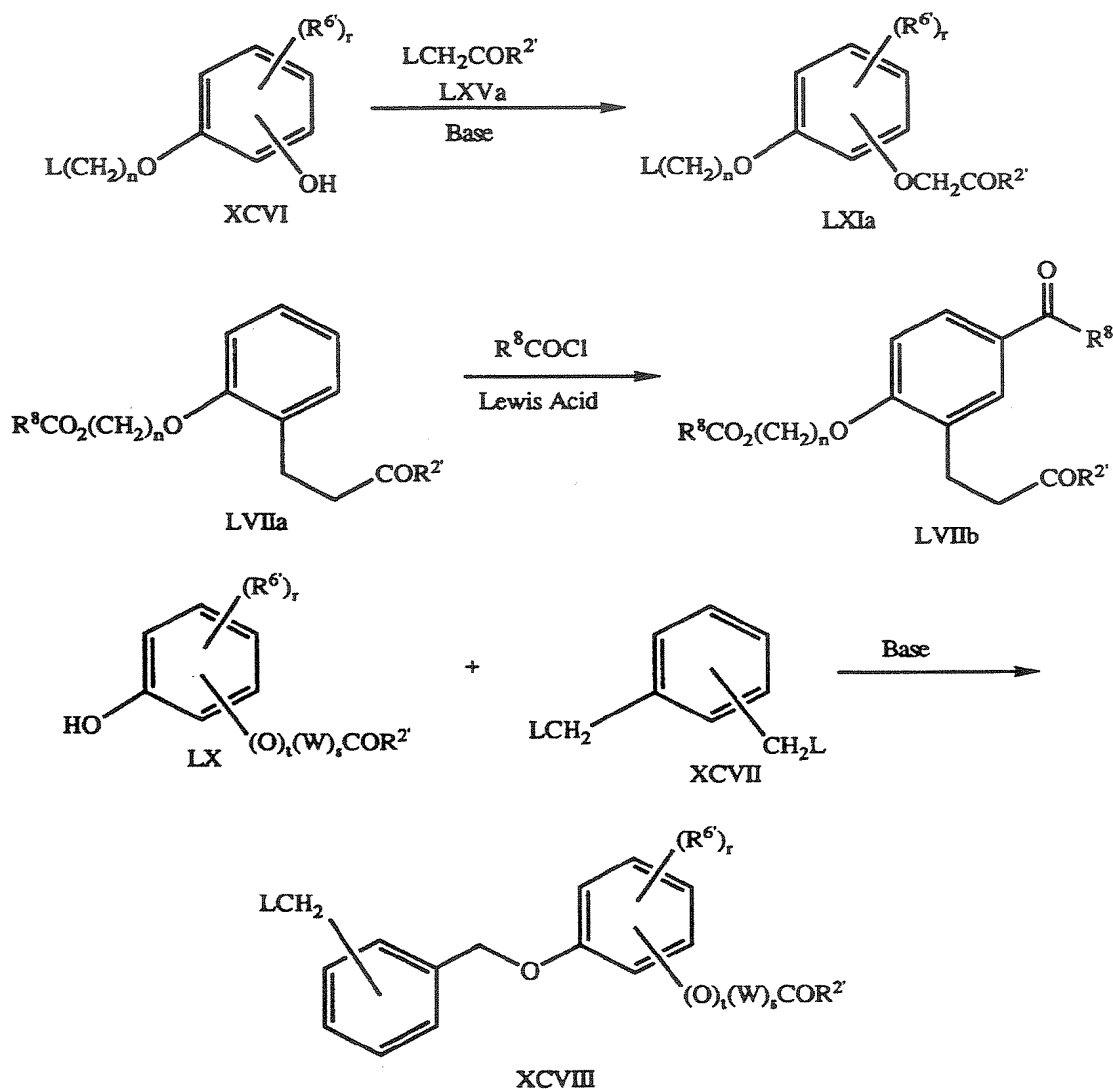


wherein  $\text{R}^{2'}$ ,  $\text{R}^7$ ,  $\text{L}$ ,  $\text{W}$ ,  $\text{M}$ ,  $n$  and  $s'$  are as previously described.

In Reaction Scheme 22, a coumarin of formula LXXIII is converted to the corresponding trifluoromethanesulfonic ester of formula LXXXIX as described in Reaction Scheme 4 for the conversion of IIa to X. The resulting compound of formula LXXXIX is recovered by conventional chromatographic methods, recrystallization or the like. Condensation of a sulfonate of formula LXXXIX with the acetylene of formula XXI is carried out as described in Reaction Scheme 4 for the conversion of X to Ig to give the corresponding adduct of formula XC which can be recovered by chromatography or the like. A compound of formula XC is converted to the corresponding phenolic cinnamate of formula XCI by alcoholysis of the

lactone ring using an alkali metal lower alkoxide in a lower alkanol solvent. The transformation is carried out as described in Reaction Scheme 18 for the conversion of LXXIV to La. A compound of formula XCI is recovered by standard chromatographic methods. Alkylation of a compound of formula XCI with a compound of formula LXV is carried out as described in Reaction Scheme 18 for the conversion of the compound of formula LXXIII to the compound of formula LXXIV and affords the compound of formula XCII which is recovered by chromatography. Catalytic hydrogenation of the compound of formula XCII using the procedure described in Reaction Scheme 14 for the conversion of XII to LIX, gives the corresponding saturated compound of formula XCIII. Removal of the protecting group R<sup>7</sup> in a compound of formula XCIII can be carried out as described in Reaction Scheme 9 for the transformation of XXVI to XXVIII and yields the corresponding alcohol of formula XCIV. The resulting compound of formula XCIV is converted to XCV as described in Reaction Scheme 9 for the conversion of XXVIII to XXX.

### Reaction Scheme 23



wherein R<sup>2'</sup>, R<sup>6'</sup>, R<sup>8</sup>, L, W, n, r, s and t are as previously described.

In Reaction Scheme 23, alkylation of a phenol of formula XCVI, which represents known compounds or compounds which can be prepared by known procedures, with an ester of formula LXVa, which also



represents known compounds, in the presence of a base gives the product of formula LXIa. This alkylation is carried out under standard conditions for effecting the alkylation of a phenol such as those described in Reaction Scheme 13 for the conversion of the compound of formula L to the compound of formula LIII. The compound of formula LXIa is recovered by conventional chromatographic methods.

5 Friedel-Crafts acylation of a diester of formula LVIIa with a carboxylic acid chloride  $R^8COCl$  gives the corresponding product of formula LVIIb. This acylation is carried out using a Lewis acid under standard Friedel-Crafts conditions such as those described in Reaction Scheme 19 for the conversion of LXXV to LXXVII. The product LVIIb is recovered by standard chromatography.

10 Alkylation of a phenol of formula LX with a compound of formula XCVII, which represents known compounds, in the presence of base, gives the corresponding product of formula XCVIII which is recovered by chromatography. This alkylation can be carried out as described in Reaction Scheme 2 for the conversion of II to V.

15

20

25

30

35

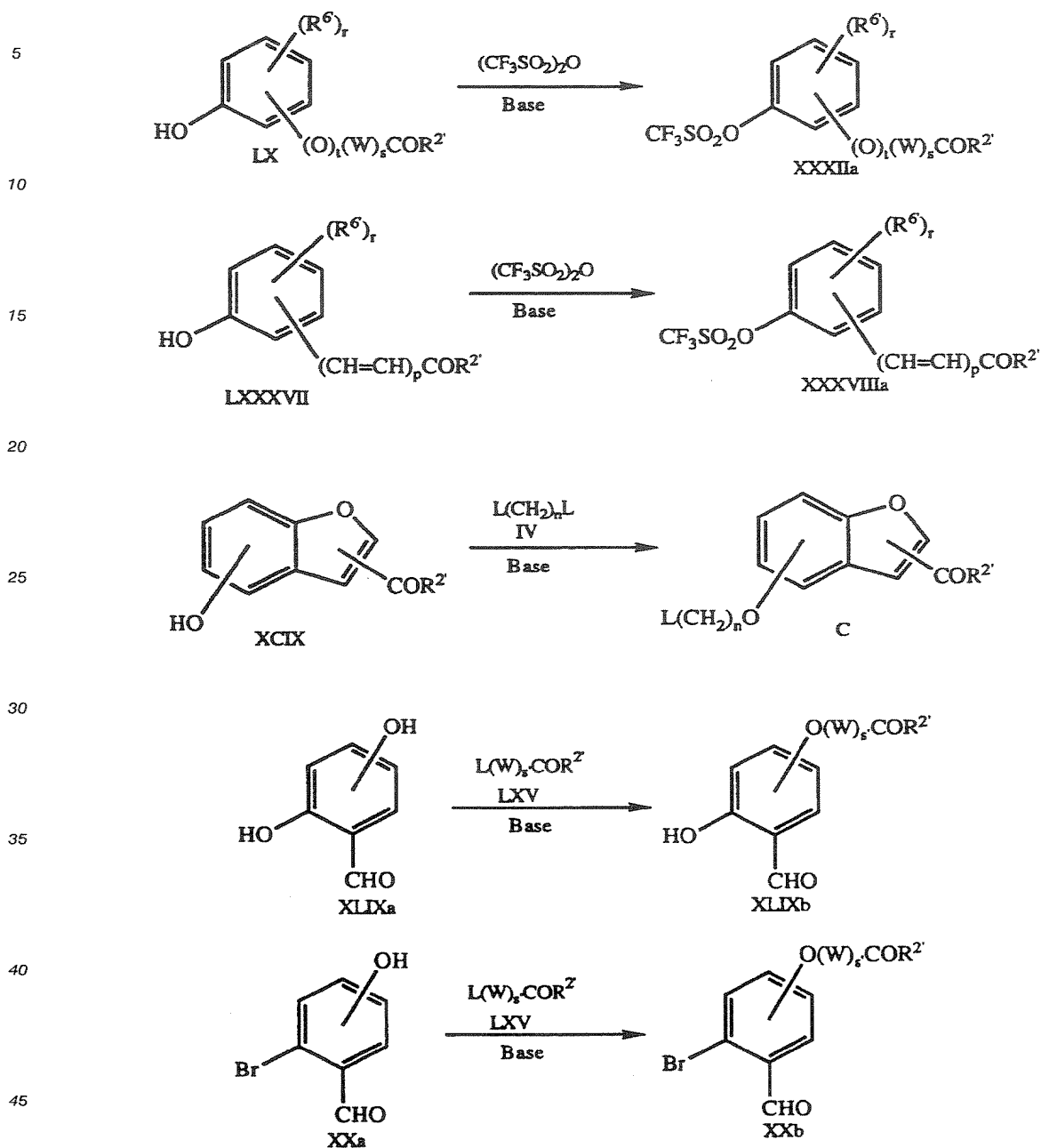
40

45

50

55

## Reaction Scheme 24



wherein  $\text{R}^2$ ,  $\text{R}^6$ , L, W, n, p, r, s, s' and t are as previously described.

In reaction Scheme 24, a phenol of formula LX is converted to the corresponding trifluoromethanesulfonate of formula XXXIIa by treatment with trifluoromethanesulfonyl anhydride in the presence of an amine base. Any conventional amine base may be utilized. Pyridine or triethylamine are preferred. This transformation is preferably carried out in dichloromethane solvent at a temperature in the range of 0° to 25 °C. The compound of formula XXXIIa can be recovered by conventional means such as chromatography. In a similar manner, the phenol of formula LXXXVII is converted to the corresponding trifluoromethanesulfonate of formula XXXVIIIa.

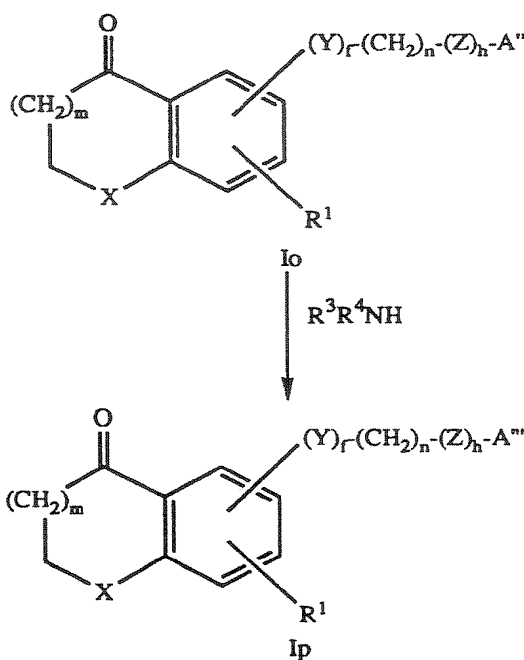
Alkylation of a hydroxybenzofurancarboxylate of formula XCIX, which represents known compounds, with a compound of formula IV in the presence of a base gives the corresponding product of formula C.

This alkylation can be carried out under standard conditions for effecting the alkylation of a phenol such as those described in Reaction Scheme 2 for the conversion of II to V. The product of formula C is isolated conventionally by chromatography.

Alkylation of a dihydroxybenzaldehyde of formula XLIXa, which represents known compounds, with one molar equivalent of a compound of formula LXV in the presence of at least two molar equivalents of a base gives the corresponding mono-alkylated product of formula XLIXb. It is preferred that an alkali metal hydride base be employed in this alkylation in a polar aprotic solvent at a temperature in the range of 25° to 80 °C. It is most preferred that this alkylation be carried out using sodium hydride in N,N-dimethylformamide at ambient temperature. The product of formula XLIXb is recovered by chromatography.

Alkylation of a bromophenol of formula XXa, which represents known compounds, with a compound of formula LXV in the presence of a base gives the corresponding product of formula XXb which is recovered by chromatography. This alkylation is carried out under standard conditions for effecting the alkylation of a phenol such as those described in Reaction Scheme 1 for the conversion of II to Ia.

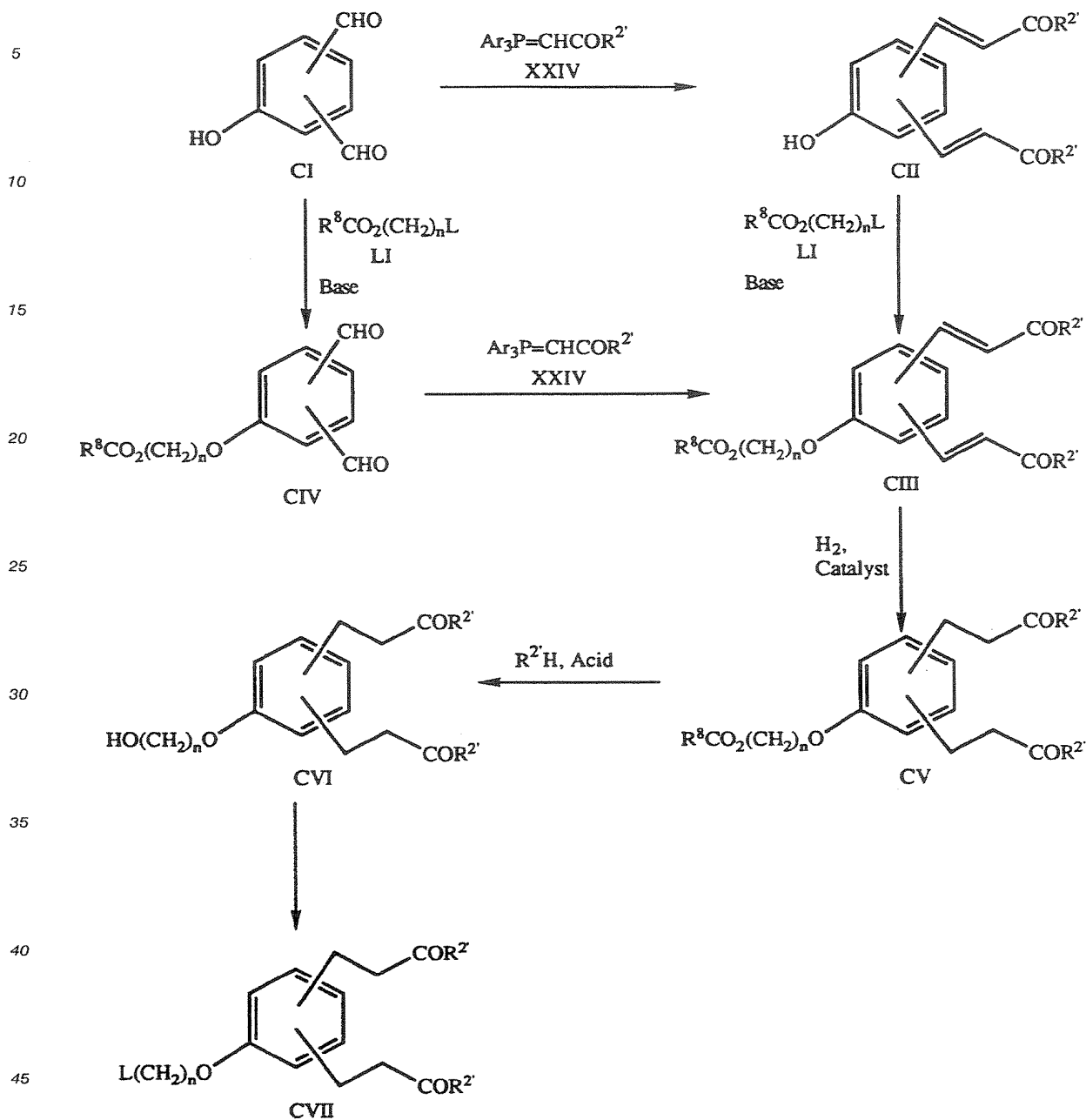
### Reaction Scheme 25



wherein A''' is -B''' or -O-B''', wherein B''' is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group -COR<sup>2'''</sup>, -(O)<sub>t</sub>-(W)<sub>s</sub>-COR<sup>2'''</sup> or -(CH=CH)<sub>p</sub>COR<sup>2'''</sup> and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)<sub>k</sub>-(W)<sub>s</sub>-E''' or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E''', provided that no more than one of said substituents is -(Q)<sub>k</sub>-(W)<sub>s</sub>-E''' or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E''', E''' is COR<sup>2'''</sup> and R<sup>2'''</sup> is NR<sup>3</sup>R<sup>4</sup>, and wherein R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, A'', Q, W, X, Y, Z, f, h, k, m, n, p, s, s', s'', s''' and t are as previously described.

In Reaction Scheme 25, an acid of formula Io is converted to the corresponding amide of formula Ip by reaction with the amine R<sup>3</sup>R<sup>4</sup>NH. This reaction can be carried out using any of the standard methods of forming amides from acids. These include treatment of the acid with 1,1'-carbonyldiimidazole and the amine or exposure of the acid to a base, a carbodiimide and the amine. It is understood that if more than one carboxyl moiety is present in the starting acid, all such groups will be converted to the corresponding amide linkage. It is preferred that the amidation reaction be performed by treating the acid of formula Io with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole, triethylamine and the amine R<sup>3</sup>R<sup>4</sup>NH in dichloromethane solution at ambient temperature. The amide of formula Ip is recovered by chromatography or recrystallization.

## Reaction Scheme 26



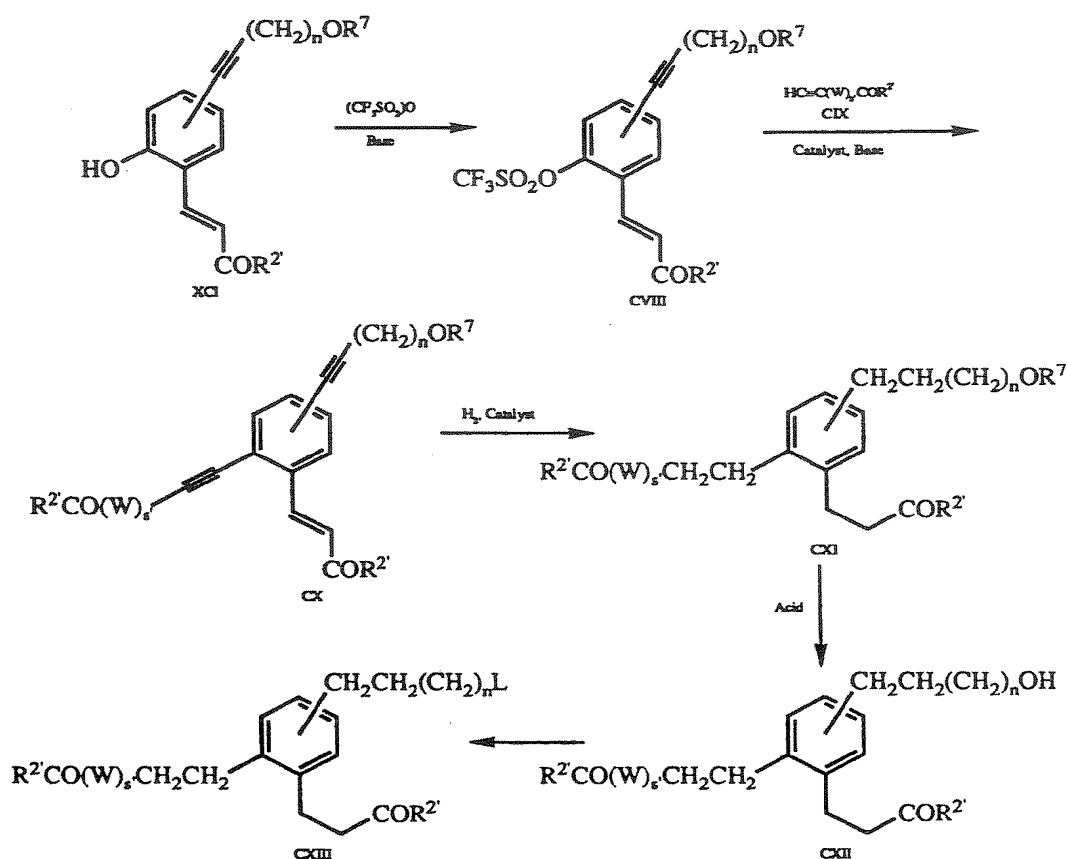
wherein Ar, R<sup>2'</sup>, R<sup>8</sup>, L and n are as previously described.

In Reaction Scheme 26, a hydroxydialdehyde of formula CI, which represents known compounds, is condensed with a phosphorane of formula XXIV using reaction conditions previously described (Reaction Scheme 9) to give the corresponding diester product of formula CII which is recovered by conventional chromatography. Alkylation of the compound of formula CII with an ester of formula LI in the presence of a base gives the product of formula CIII. This alkylation is carried out under standard conditions for effecting the alkylation of a phenol such as those described previously in Reaction Scheme 13. The compound of formula CIII is recovered by conventional chromatographic methods.

Alternatively, the compound of formula CIII can be produced from the compound of formula CI by reversing this order of reactions, in other words, by first conventionally alkylating the compound of formula

CI with the compound of formula LI to give the compound of formula CIV. The compound of formula CIV is then condensed with a phosphorane of formula XXIV to give the compound of formula CIII. The conditions required for effecting these transformations are as described previously. Catalytic hydrogenation of the compound of formula CIII under conditions described previously gives the corresponding saturated triester of formula CV. The compound of formula CV is converted to the corresponding hydroxy diester of formula CVI by removal of the ester protecting group  $R^8CO$  using an acidic catalyst. This transformation is carried out as described in Reaction Scheme 13 for the conversion of the compound of formula LIII to the compound of formula LIV. The compound of formula CVI is recovered by conventional chromatography and is converted to the corresponding derivative CVII using standard methods known in the art for transforming hydroxy groups into leaving groups such as those described in Reaction Scheme 9 for the conversion of a compound of formula XXVIII to a compound of formula XXX.

## Reaction Scheme 27

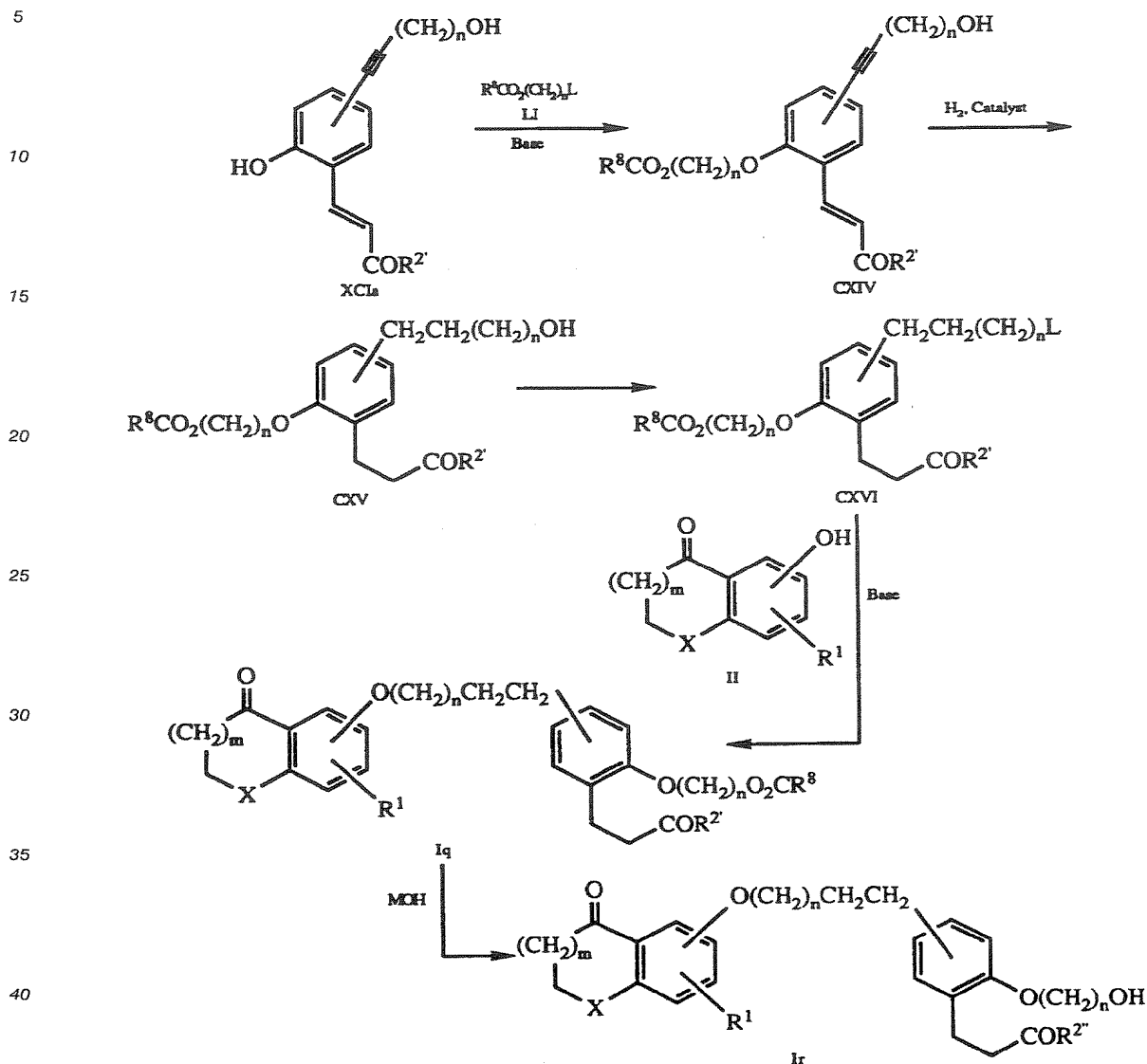


wherein  $R^2$ ,  $R^7$ ,  $L$ ,  $W$ ,  $n$ , and  $s'$  are as previously described.

In Reaction Scheme 27, a hydroxy cinnamate of formula XCI (Reaction Scheme 22) is converted to the corresponding trifluoromethanesulfonate CVIII as described in Reaction Scheme 4 for the conversion of a compound of formula IIa to a compound of formula X. The compound of formula CVIII is recovered by conventional chromatographic methods. Condensation of the sulfonate of formula CVIII with the acetylenic ester of formula CIX, which represents known compounds, is carried out as described in Reaction Scheme 4 for the conversion of a compound of formula X to the corresponding compound of formula Ig giving the adduct of formula CX which is recovered by chromatography. The compound of formula CX is converted to the corresponding saturated diester of formula CXI by conventional catalytic hydrogenation and is recovered by standard chromatographic methods. Removal of the protecting group  $R^7$  in the compound of formula CXI is carried out as described in Reaction Scheme 9 for the transformation of a compound of formula XXVI to the corresponding compound of formula XXVIII, and affords the corresponding hydroxy diester of formula CXII. The compound of formula CXII is converted to the compound of formula CXIII as described in

Reaction Scheme 9 for the conversion of the compound of formula XXVIII to the compound of formula XXX.

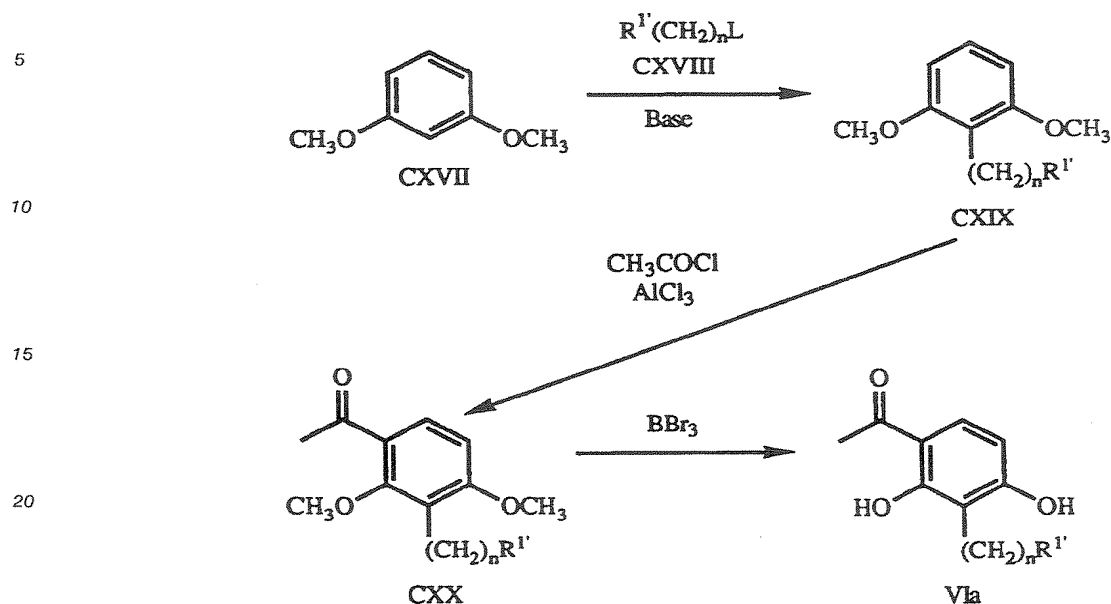
### Reaction Scheme 28



wherein  $R^1$ ,  $R^2$ ,  $R^2'$ ,  $R^8$ ,  $L$ ,  $M$ ,  $X$ ,  $m$ , and  $n$  are as previously described.

In Reaction Scheme 28, alkylation of a dihydroxy cinnamate of formula XCIa with the compound of formula LI gives the corresponding hydroxy diester of formula CXIV. This alkylation is carried out as described in Reaction Scheme 13 for the conversion of a compound of formula L to the corresponding compound of formula LIII. The compound of formula CXIV, which is recovered by conventional chromatography, is catalytically hydrogenated under conditions described previously giving the corresponding saturated compound of formula CXV. The compound of formula CXV is converted to the compound of formula CXVI as described in Reaction Scheme 9 for the conversion of a compound of formula XXVIII to the corresponding compound of formula XXX. Alkylation of a compound of formula II with a corresponding compound of formula CXVI using conditions described in Reaction Scheme 1 gives the product diester of formula Iq which is recovered by conventional chromatography. Saponification of the compound of formula Iq using conditions described in Reaction Scheme 1 gives the corresponding hydroxy acid product of formula Ir which is recovered by conventional recrystallization or chromatography.

## Reaction Scheme 29

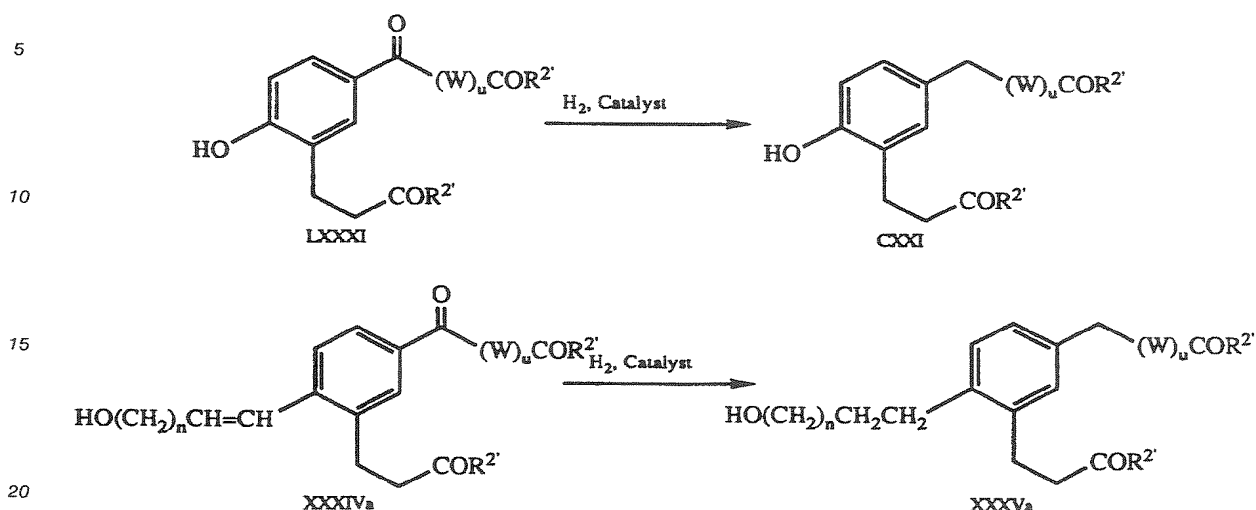


wherein R<sup>1</sup> is hydrogen, lower alkenyl, cycloalkyl or aryl and L and n are as previously described.

In Reaction Scheme 29, 1,3-dimethoxybenzene, a known compound of formula CXVII, is converted into the product of formula CXIX by first treatment with a strong base followed by an alkylating agent of formula CXVIII which represents known compounds. It is preferred that the base used in this alkylation be an organolithium species such as methyl lithium, phenyllithium, n-butyllithium and the like and that the alkylation be carried out in an inert ether solvent. It is particularly preferred that the alkylation be carried out using n-butyllithium in tetrahydrofuran at a temperature of from -20 °C to room temperature. The product of formula CXIX is recovered by conventional chromatography.

Acetylation of the compound of formula CXIX is carried out under standard Friedel-Crafts conditions such as those described in Reaction Schemes 19 and 23 giving the corresponding acetophenone product of formula CXX which is recovered by chromatography. Treatment of the compound of formula CXX under standard demethylation conditions such as using boron tribromide in dichloromethane solution at from -50 °C to room temperature gives the corresponding dihydroxyacetophenone product of formula VIa which is recovered by conventional chromatography or recrystallization.

## Reaction Scheme 30



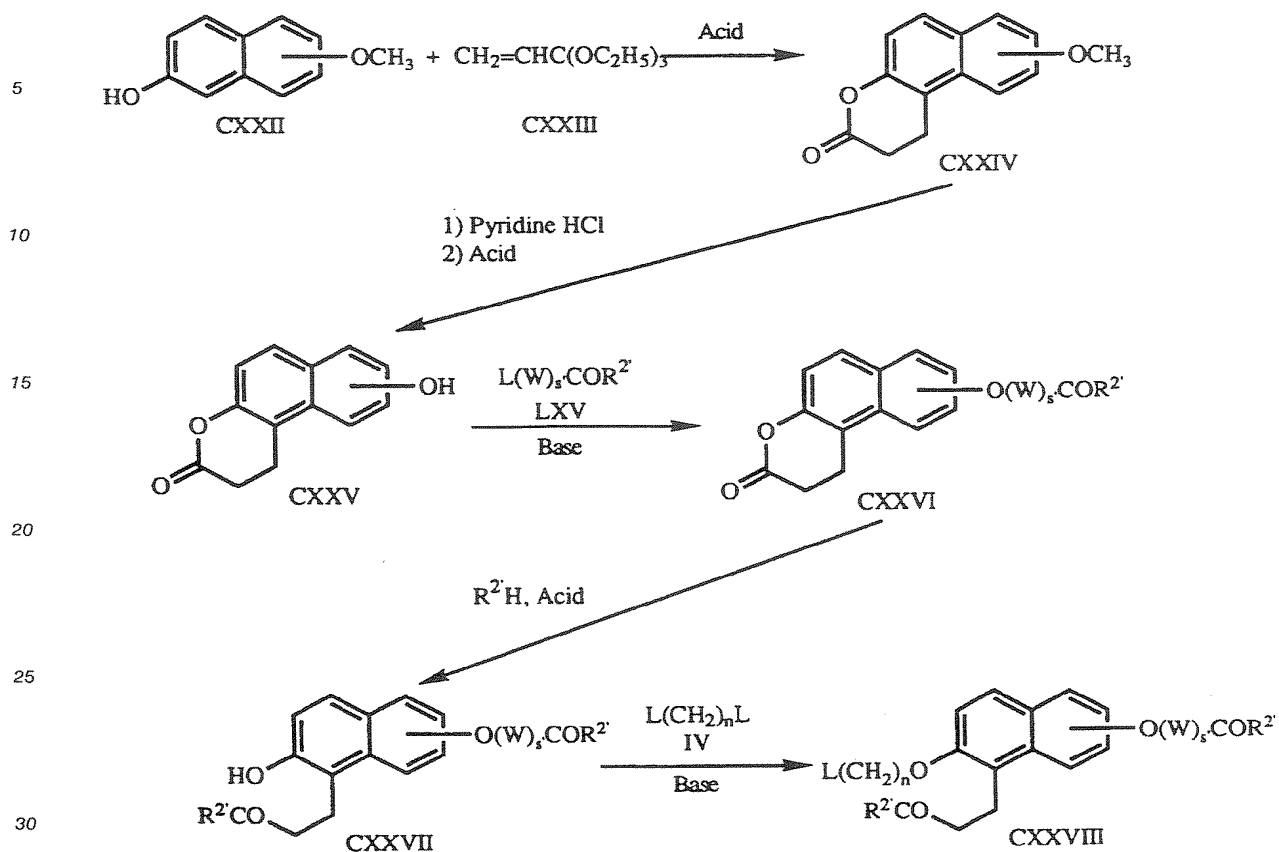
wherein  $R^{2'}$ , W, n and u are as previously described.

In Reaction Scheme 30, a compound of formula LXXXI from Reaction Scheme 19 is catalytically hydrogenated to give the corresponding compound of formula CXXI. This reduction is carried out under standard conditions for effecting the hydrogenolytic removal of the oxygen atom from aromatic carbonyl groups such as reduction over a noble metal catalyst. It is preferred that this reduction be carried out using palladium on carbon as the catalyst. This hydrogenation can be carried out in conventional solvents such as ethanol, ethyl acetate or acetic acid. It is preferred that this hydrogenation be carried out in acetic acid under a hydrogen pressure of from 96 to 345 kPa and at room temperature to 50 ° C. The compound of formula CXXI is recovered by conventional chromatography.

Under similar reaction conditions, catalytic hydrogenation-hydrogenolysis of a compound of formula XXXIVa (Reaction Scheme 10) gives the corresponding compound of formula XXXVa. In this case, the olefinic function present in the starting compound is also reduced.



## Reaction Scheme 31



wherein L, W,  $R^2$ , n and s' are as previously described.

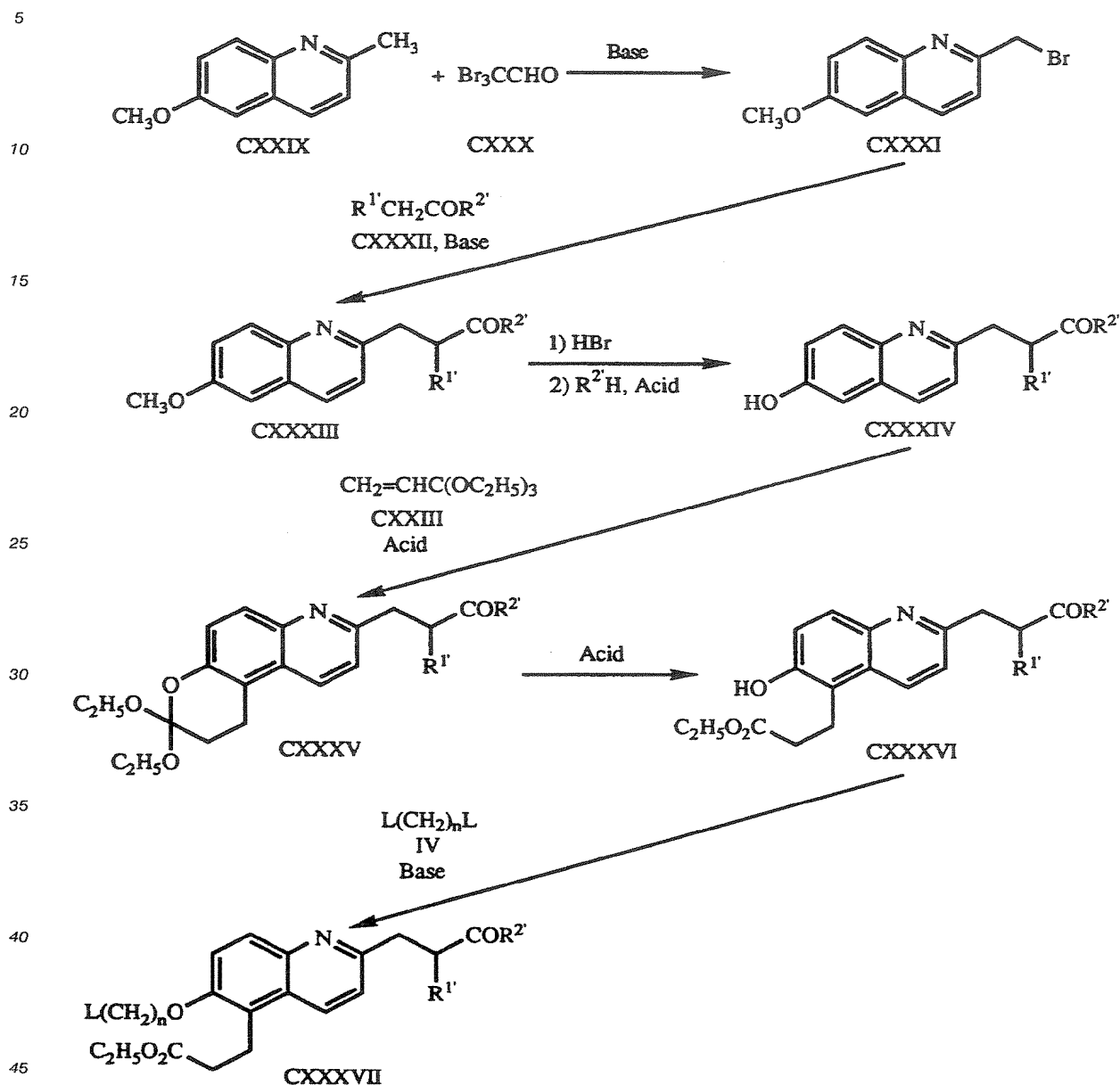
In Reaction Scheme 31, a methoxynaphthalenol of formula CXXII which represents known compounds, is allowed to react with triethyl orthoacrylate represented by formula CXXIII, also a known compound, in the presence of an acid catalyst, to effect a Claisen rearrangement. It is preferred that a carboxylic acid be used as the catalyst in this transformation. It is most preferred that the acid catalyst be trimethylacetic acid. This reaction can be carried out in an inert solvent such as an aromatic hydrocarbon at a temperature in the range of 100° to 150 °C. It is preferred that this reaction be carried out in refluxing toluene. The initial product of this reaction is an ortho ester which is not recovered but, rather, directly treated with dilute acid to give a mixture of the lactone product of formula CXXIV and the corresponding open hydroxy ethyl ester. This mixture upon exposure to a strong acid, preferably para-toluenesulfonic acid, gives pure lactone CXXIV which is recovered by conventional chromatography or recrystallization. The compound of formula CXXIV is demethylated under standard conditions for effecting such a dealkylation, preferably, by fusion with pyridine hydrochloride. It is preferred that this demethylation be carried out at a temperature in the range of 200° to 250 °C. Since these demethylation conditions also cause cleavage of the lactone ring, the crude product is treated with a strong acid in order to recycle the isolated hydroxy acid. It is preferred that this cyclization be carried out by treatment of the demethylation product with paratoluenesulfonic acid in refluxing toluene. The product of formula CXXV is recovered by conventional chromatography or recrystallization.

Alkylation of the compound of formula CXXV with the compound of formula LXV is carried out as described in Reaction Scheme 16 for the conversion of a compound of formula LXIV to the corresponding compound of formula LXVI, giving the product of formula CXXVI which is recovered by conventional chromatography.

The compound of formula CXXVI is converted to the corresponding compound of formula CXXVII as described in Reaction Scheme 16 for the conversion of a compound of formula LXVI to the corresponding compound of formula LXVII. The compound of formula CXXVII is recovered by conventional chromatography and is converted to the compound of formula CXXVIII as described in Reaction Scheme 16 for the conversion of the compound of formula LXVII to the compound of formula LXIXa. The compound of formula

CXXVIII is recovered by conventional chromatography.

### Reaction Scheme 32



wherein  $\text{R}^1$ ,  $\text{R}^2$ , L and n are as previously described.

In Reaction Scheme 32, 6-methoxy-2-methylquinoline, the known compound of formula CXXIX, is allowed to react with tribromoacetaldehyde, also a known compound of formula CXXX, in the presence of a base catalyst to give the product of formula CXXXI. It is preferred that the catalyst in this reaction be an amine base, specifically pyridine, and that the reaction be carried out in a polar, aprotic solvent, preferably N,N-dimethylformamide, at a temperature in the range of 50° to 100 °C. The compound of formula CXXXI is recovered by conventional chromatography or recrystallization, and is converted to a compound of formula CXXXIII by alkylation of the enolate derived from a known ester of the formula CXXXII. The required enolate is generated by treatment of the ester CXXXII with a strong base. It is preferred that this base be the alkali metal salt of a di-lower alkyl amine, specifically lithium diisopropylamide. The alkylation reaction is carried out in an inert solvent, preferably tetrahydrofuran, at a temperature in the range of from -78° to 25

° C. The product of formula CXXXIII is recovered by conventional chromatography and is demethylated by treatment with a strong acid, preferably 48% aqueous hydrobromic acid, at reflux.

Since these conditions also induce ester hydrolysis, the crude demethylation product is reesterified by treatment with an alcohol R<sup>2</sup>H in the presence of an acid catalyst, preferably acetyl chloride, giving the corresponding phenol product CXXXIV which is recovered by conventional chromatography or recrystallization. The compound of formula CXXXIV is allowed to react with triethyl orthoacrylate, the compound of formula CXXIII, using the procedure described in Reaction Scheme 31 for the conversion of a compound of formula CXXII to the compound of formula CXXIV. In this case, however, the ortho ester of formula CXXXV rather than the corresponding lactone is recovered. A compound of formula CXXXV is converted to the corresponding compound of formula CXXXVI by treatment with a strong acid, preferably para-toluenesulfonic acid, in a mixture of water and an organic solvent, preferably diethyl ether, at room temperature. The compound of formula CXXXVI is recovered by conventional chromatography and is converted to the compound of formula CXXXVII as described in Reaction Scheme 16 for the conversion of a compound of formula LXVII to the corresponding compound of formula LXIXa. Compound CXXXVII is recovered by conventional chromatography.

The invention also relates to salts of the compounds of formula I when they contain an acidic functionality which lends itself to salt formation with a base. Salts of compounds of formula I which have a carboxy group are prepared by the reaction with a base having a non-toxic, pharmacologically acceptable cation. In general, any base which will form a salt with a carboxylic acid and whose pharmacological properties will not cause an adverse physiological effect is within the scope of this invention.

Suitable bases thus include, for example, the alkali metal and alkaline earth metal hydroxides, carbonates or the like, for example, calcium hydroxide, sodium hydroxide, sodium carbonate, potassium carbonate or the like, ammonia, primary, secondary and tertiary amines such as monoalkylamines, dialkylamines, trialkylamines, for example, methylamine, diethylamine, triethylamine or the like, nitrogen containing heterocyclic amines, for example, piperidine or the like. A salt thus produced is the functional equivalent of the corresponding compound of formula I wherein R<sup>2</sup> is hydroxy and one skilled in the art will appreciate that the variety of salts embraced by the invention is limited only by the criterion that a base employed in forming the corresponding salts be both non-toxic and physiologically acceptable.

The useful activity of the compounds of formula I as leukotriene B<sub>4</sub> antagonists can be demonstrated as hereinafter set forth.

#### Methodology:

##### LTB<sub>4</sub> Receptor Binding Assay

Binding assays can be performed in microtiter wells. Isolated human neutrophils in Gey's salt solution are incubated on ice for 45 minutes with 0.5nM <sup>3</sup>H-LTB<sub>4</sub> in the presence or absence of test compounds. Assays are terminated by adding 12 ml ice cold 50 mM Tris (pH 7.4) followed by rapid filtration under vacuum through GF/C filters. Radioactivity is determined by scintillation counting. Non specific binding is defined as the binding not displaced by 100 fold excess of unlabelled LTB<sub>4</sub>. Specific binding is defined as the difference between total binding and non-specific binding. Non linear analysis of the binding data is performed using LIGAND (Munson and Rodbard, 1980). K<sub>i</sub> (Inhibition Constant) values were determined using the Cheng-Prusoff relationship (Cheng and Prusoff, 1973).

When representative compounds of formula I of the invention were tested, the results as set forth in Table I and expressed as inhibition of <sup>3</sup>H-LTB<sub>4</sub> binding were obtained.

TABLE I

**EXAMPLE    TEST    COMPOUND**

**HUMAN NEUTROPHIL  
CELLS (Ki,nM)**

4	2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid	29
8	2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyll]-benzenepropanoic acid	63
10	2-[[5-(5-Oxo-1-propyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]pentyloxy]-benzenepropanoic acid	78
11	rac.-6-Acetyl-7-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid	105
13	[2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-phenoxy]acetic acid	70
17	5-Chloro-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid	36
19	7-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-2-benzofurancarboxylic acid	250
20	5-[(3-Carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	2
22	5-[(3-Carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyloxy]benzenepropanoic acid	3
24	5-[(3-Carboxyphenyl)carbonyl]-2-[4-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]butoxy]benzenepropanoic acid	15

EXAMPLE	TEST COMPOUND	HUMAN NEUTROPHIL CELLS(Ki,nM)
26	5-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-2-benzofuran-2-carboxylic acid	270
33	5-Acetyl-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	10
37	2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	10
39	2-[3-[[[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]methyl]phenylmethoxy]benzenepropanoic acid	100
40	2-[5-[(2,3-Dihydro-3-oxo-7-propylbenzofuran-6-yl)oxy]pentyloxy]benzenepropanoic acid	75
47	5-(3-Carboxypropoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	3
54	5-(3-Carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	1
58	5-(4-Carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid hemihydrate	4
62	6-(4-Carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	0.8
68	3-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	60
73	2-[5-[(3,4-Dihydro-4-oxo-8-(phenylmethyl)-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	150

**EXAMPLE    TEST COMPOUND    HUMAN NEUTROPHIL  
CELLS(Ki.nM)**

79	2-[5-[(5-Oxo-2-propyl-5,6,7,8-tetrahydro-1-naphthalenyl) oxy]pentyloxy]-benzenepropanoic acid	1500
81	5-[(3-Carboxyphenyl)carbonyl]-2-[7-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]heptyloxy]benzenepropanoic acid	3
83	5-[(3-Carboxyphenyl)carbonyl]-2-[8-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]octyloxy]benzenepropanoic acid	3
85	5-[(4-Carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	3
87	3-(2-Carboxyethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-8-oxobenzenepentanoic acid	3
89	3-(2-Carboxyethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-γ-oxobenzenebutanoic acid	4
92	5-[2-(2-Carboxyphenyl)-1-oxoethyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	5
95	5-[[2-(Carboxymethyl)phenyl]carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	8
99	5-[(3-Carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	1
101	(E)-5-[(3-Carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]-1-hexenyl]benzenepropanoic acid	4
106	2-[6-(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)hexyloxy]-benzenepropanoic acid	20

**HUMAN NEUTROPHIL  
CELLS(Ki,nM)**

**EXAMPLE TEST COMPOUND**

107	2-[6-(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-5-hexynyloxy]-benzenepropanoic acid	50
109	(E)-3-[2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]-pentyloxy]phenyl]-2-propenoic acid	80
114	(E)-4-[3-(2-Carboxyethenyl)-4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]phenoxy]butanoic acid	1
118	2-[5-[(3,4-Dihydro-4-oxo-8-pentyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid	607
126	2-(4-Carboxybutoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	1.5
138	4-(3-Carboxypropoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	88

5  
10  
15  
20  
25  
30  
35  
40  
45  
50  
55

EXAMPLE	TEST COMPOUND	HUMAN NEUTROPHIL CELLS (K1mM)
145	2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenebutanoic acid	30
147	2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepentanoic acid	200
152	2-(Carboxymethoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	1
157	2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	1
163	4-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-1,3-benzenedipropanoic acid	3
169	2-(2-Carboxyethyl)-3-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenhexanoic acid	1
174	2-[(4-Carboxy-4-methylpentyloxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	1
180	2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-6-[(5-hydroxypentyl)oxy]benzenepropanoic acid	1
184	2-[(7-Carboxyheptyloxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	1
188	2-[(8-Carboxyocetyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	3
195	2-[[5-[[3,4-Dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl]oxy]pentyloxy]benzenepropanoic acid	95



EXAMPLE	TEST COMPOUND	HUMAN NEUTROPHIL CELLS (K <sub>10</sub> M)
196	2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-oxy]hexyl]-6-[[5-(dimethylamino)-5-oxopentyl]oxy]-N,N-dimethylbenzenepropanamide	200
200	2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid	1
205	2-(3-Carboxypropoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	1
206	2-[(5-Carboxypentyl)oxy]-6-[6-[(5,6,7,8-tetrahydro-5-oxo-1-propyl-2-naphthalenyl)oxy]hexyl]benzenepropanoic acid	3
211	3-(2-Carboxyethyl)-4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-8-oxobenzopentanoic acid	0.8
215	3-(2-Carboxyethyl)-4-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepentanoic acid	3
219	3-(2-Carboxyethyl)-4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepentanoic acid	1
226	7-(Carboxymethoxy)-2-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-1-naphthalenepropanoic acid	1
231	6-(Carboxymethoxy)-2-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-1-naphthalenepropanoic acid	0.8
238	6-[[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-2,5-quinolinedipropanoic acid	2

#### 50 Isolation of Intact Neutrophils

Human neutrophils are prepared from citrated or heparinized blood. The blood was diluted 1:1 with Hank's balanced salt solution (HBSS) minus calcium and magnesium and underlayered with 10 ml lymphocyte separation medium (Organon Teknika), followed by centrifugation at 500 x g for 30 min, at room temperature. Supernatants are removed down to the red blood cell pellet. HBSS minus calcium and magnesium are added to give 25 ml. To this are added 25 ml 6% dextran in 0.85% NaCl. Samples are mixed and allowed to stand 20 min at room temperature. Supernatants are removed and centrifuged at 500 x g for 5 min at 4 °C. Pellets are resuspended with 20 ml 0.2% saline for 20 sec followed by the addition of

20 ml 1.6% saline. Samples are centrifuged at 500 x g for 5 min at 4 ° C. The lysis is repeated and the cells (90-95% neutrophils) are resuspended at  $2 \times 10^6$  cell/ml in GEY's salt solution.

#### Calcium Flux Assay

LTB<sub>4</sub> induced changes in intracellular calcium concentration are measured using Fura2 labelled human neutrophils. Cells at a concentration of  $2-5 \times 10^6$ /ml are labelled with 5 μM Fura2 for 30 minutes in Hank's balanced salt solution without calcium and magnesium. The cells are washed and resuspended at a final concentration of  $1-2 \times 10^7$  cells/ml in Gey's solution. Calcium fluxes are initiated by the addition of 2.4nM LTB<sub>4</sub>. Test compounds at appropriate concentrations are added to the cells just prior to the addition of LTB<sub>4</sub>. IC<sub>50</sub> values are determined as the concentration of compound required to give 50% inhibition of the LTB<sub>4</sub>-induced calcium flux. Fluorescence measurements are made in a Perkin Elmer model LS-5B spectrofluorimeter at a temperature setting of 37 ° C. Calcium concentrations are determined using the ratio method (ratio of cell fluorescence to media fluorescence).

When representative compounds of formula I of the invention were tested, the results set forth in Table II and expressed as inhibition of LTB<sub>4</sub> mediated calcium fluxes in human neutrophils, were obtained.

TABLE II

TEST COMPOUND	CALCIUM FLUX (IC <sub>50</sub> ,nM)
2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	26
rac.-6-Acetyl-7-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid	300
5-Chloro-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	70
5-[(3-Carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	1
5-[(3-Carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyloxy]benzenepropanoic acid	1
5-[(3-Carboxyphenyl)carbonyl]-2-[4-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]butoxy]benzenepropanoic acid	11
5-(3-Carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	2
2-(4-Carboxybutoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	2
2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	1
2-(Carboxymethoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	3
2-(2-Carboxyethyl)-3-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenehexanoic acid	1
2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-6-[(5-hydroxypentyl)oxy]benzenepropanoic acid	1

#### LTB<sub>4</sub> Induced Skin Inflammation

Skin inflammation is induced in the hairless guinea pig by the intradermal injection of 50 μl Gey's salt solution/10% DMSO containing 120 ng LTB<sub>4</sub>. Injections are performed along the dorsal skin of the animals. Test compounds are administered at various times by co-injection, intravenous or oral administration. The test animals are euthanized four to six hours after the LTB<sub>4</sub> injection and uniform skin punches are prepared from the injection sites. Punches are homogenized in 0.5% hexadecyltrimethyl ammonium bromide for one minute and centrifuged for 20 minutes at 14,000 x g. Leukocyte accumulation is measured by assaying for myeloperoxidase activity in a kinetic assay using dimethoxybenzidine as the substrate. Normal skin shows

myeloperoxidase levels of 0.02-0.04 U/punch. Skin injected with 120 ng LTB<sub>4</sub> can show myeloperoxidase levels of 0.30-0.40 U/punch. LTB<sub>4</sub> induced leukocyte accumulation is confirmed histologically in hematoxylin/eosin stained sections. ID<sub>50</sub> values are determined as the dose of test compound required to give 50% inhibition of the LTB<sub>4</sub>-induced skin inflammation.

- 5 5-[(3-Carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid (Example 20) gave ID<sub>50</sub>'s of 100 ng by co-injection with LTB<sub>4</sub>, 6mg/kg by intravenous administration at the time of the intradermal LTB<sub>4</sub> injection and 30 mg/kg by the oral route.
- 5-(3-Carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid (Example 54) gave ID<sub>50</sub>'s of 10 ng by co-injection with LTB<sub>4</sub> and 5 mg/kg by the oral route.
- 10 3-(2-Carboxyethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-δ-oxobenzenepentanoic acid (Example 87) gave an ID<sub>50</sub> of 20 ng by co-injection.
- 6-(4-Carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid (Example 62) gave an ID<sub>50</sub> of 35 ng by co-injection.
- 15 5-[(3-Carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid (Example 99) gave an ID<sub>50</sub> of 20 ng by co-injection.

#### Guinea Pig Bronchoconstriction (in vivo)

- Male guinea pigs (Hartley strain) weighing 300 to 500 g are anesthetized with urethane (2g/kg)
- 20 intraperitoneally and a polyethylene cannula is inserted into the jugular vein for drug administration. Tracheal pressure is recorded from a cannula inserted into the trachea and connected to a Gould P23ID pressure transducer. After surgical preparation of the animals, a period of time is allowed for pulmonary functions to stabilize. The test compound is administered intravenously five minutes prior to leukotriene B<sub>4</sub> administration according to the following protocol: Animals are paralyzed with succinylcholine (1.2 mg/kg
- 25 i.v.) and mechanically respirated (Harvard rodent respirator) at 40 breaths/minute and 2.5 cc tidal volume. Propranolol (0.1mg/kg) is then administered intravenously one minute prior to leukotriene B<sub>4</sub> administration. Animals are then challenged with an intermediate constrictory dose of leukotriene B<sub>4</sub> (1μg/kg) delivered intravenously.

- 30 The change (cm H<sub>2</sub>O) between pre and peak ventilatory pressure readings is averaged for five control and five drug treated animals. The percent inhibition is calculated from the formula:

$$((\text{Control} - \text{Drug Treated})/\text{Control}) \times 100$$

- When various drug concentrations are tested, the percent inhibition at each concentration is plotted as log
- 35 concentration (abscissa) versus percent inhibition (ordinate) and the ID<sub>50</sub> is determined from linear regression analysis as the dose of test compound causing 50% inhibition of LTB<sub>4</sub>-induced bronchoconstriction.

When representative compounds of formula I of the invention were utilized as the test compounds the following results were obtained:

40

45

50

55

TABLE III

EXAMPLE	NAME	ID <sub>50</sub> (mg/kg), i.v.	ID <sub>50</sub> (mg/kg), p.o.
4	2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	0.66	>10
10	2-[[5-(5-Oxo-1-propyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]pentyloxy]benzenepropanoic acid	2.08	
13	[2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]phenoxy]acetic acid	1.85	
17	5-Chloro-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	2.02	
20	5-[(3-Carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	1.46	
33	5-Acetyl-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	1.80	
37	2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-oxy]hexyl]benzenepropanoic acid	0.45	>10
39	2-[3-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-oxy]methyl]phenylmethoxy]benzenepropanoic acid	5.40	
47	5-(3-Carboxypropoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid	3.66	
54	5-(3-Carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	0.01	8.70
58	5-(4-Carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid hemihydrate	5.09	

EXAMPLE	NAME	ID <sub>50</sub> (mg/kg), i.v.	ID <sub>50</sub> (mg/kg), p.o.
62	6-(4-Carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepropanoic acid	2.06	
68	3-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-oxy]pentyl]oxy]benzenepropanoic acid	3.56	
73	2-[5-[[3,4-Dihydro-4-oxo-8-(phenylmethyl)-2H-1-benzopyran-7-yl]oxy]pentyl]oxy]benzenepropanoic acid	0.13	>10
85	5-[(4-Carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepropanoic acid	6.23	
87	3-(2-Carboxyethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-8-oxobenzenepentanoic acid	4.41	>10
89	3-(2-Carboxyethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-γ-oxobenzenebutanoic acid	4.33	
118	2-[5-[(3,4-Dihydro-4-oxo-8-pentyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepropanoic acid	0.18	>10
126	2-(4-Carboxybutoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	0.12	0.54
145	2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenebutanoic acid	0.56	>10
147	2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepentanoic acid	1.18	
152	2-(Carboxymethoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	2.00	

EXAMPLE	NAME	ID <sub>50</sub> (mg/kg) i.v.	ID <sub>50</sub> (mg/kg) p.o.
157	2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	0.07	0.27
163	4-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-oxy]pentyl]oxy]-1,3-benzenedipropanoic acid	3.11	
169	2-(2-Carboxyethyl)-3-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenhexanoic acid	0.13	4.40
174	2-[(4-Carboxy-4-methylpentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	0.22	1.10
180	2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-oxy]hexyl]-6-[(5-hydroxypentyl)oxy]benzenepropanoic acid	0.14	4.80
184	2-[(7-Carboxyheptyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	0.17	
188	2-[(8-Carboxyoctyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	0.90	
195	2-[5-[(3,4-Dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepropanoic acid	0.04	5.80
196	2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-oxy]hexyl]-6-[[5-(dimethylamino)-5-oxopentyl]oxy]-N,N-dimethylbenzenepropanamide	0.62	
200	2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	0.06	0.16

EXAMPLE	NAME	ID <sub>50</sub> (mg/kg), i.v.	ID <sub>50</sub> (mg/kg), p.o.
205	2-(3-Carboxypropoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid	0.26	
206	2-[(5-Carboxypentyl)oxy]-6-[6-[(5,6,7,8-tetrahydro-5-oxo-1-propyl-2-naphthalenyl)oxy]hexyl]benzenepropanoic acid	0.12	
211	3-(2-Carboxyethyl)-4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-8-oxobenzenepentanoic acid	2.39	
215	3-(2-Carboxyethyl)-4-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepentanoic acid	0.24	4.65
219	3-(2-Carboxyethyl)-4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepentanoic acid	0.08	>10
226	7-(Carboxymethoxy)-2-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-1-naphthalene-propanoic acid	4.40	
231	6-(Carboxymethoxy)-2-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-1-naphthalene-propanoic acid	1.36	
238	6-[[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-2,5-quinolinedipropanoic acid	1.24	

# Acetic acid colitis.

Male Wistar rats, weighing 175-225 g, are pretreated with test compound at 10mg/kg, twice daily for 3 days (72 hours) prior to the evaluation of colitis. Colitis is induced after 2 days (48 hours) with an enema of 2ml of 3.5% acetic acid, the acetic acid is neutralized after 10 seconds by 3 ml of phosphate-buffered saline, pH 7.4. After 3 days (72 hours), animals are sacrificed and myeloperoxidase activity in mucosal

scrapings is determined as described in the skin inflammation model. Myeloperoxidase levels are presented as Unit/gm mucosa.

Results obtained in this test are set forth below.

5

Acetic Acid	46.8 +/-7.4	N = 10
control	6.8 +/-0.9	N = 10

10

5-(3-Carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl)-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid (Example 54)

19.5 +/- 3.9 N = 10 (68 % inhibition).

#### References:

15

Cheng, Y. and Prusoff, W. H. (1973) Relationship between the inhibition constant ( $K_i$ ) and the concentration of inhibitor which causes 50% inhibition ( $I_{50}$ ) of an enzymatic reaction, *Biochem. Pharmacol.*, **22**, 3099-3108.

20

Munson, P.J. and Rodbard, D. (1980) LIGAND: A versatile computerized approach for the characterization of ligand binding systems, *Anal. Biochem.*, **107**, 220-239.

25

In the practice of the invention, the dose of a compound of formula I or a salt thereof to be administered and the frequency of administration will be dependent on the potency and duration of activity of the particular compound of formula I or salt to be administered and on the route of administration, as well as the severity and nature of the condition and age of the mammal to be treated and the like. Oral doses of a compound of formula I or a salt thereof contemplated for use in practicing the invention can be in the range of from 2 mg to about 2 g per day, preferably about 2 mg to about 1 g per day, either as a single dose or in divided doses.

The examples which follow further illustrate the invention.

30

A compound of formula I or a salt or a composition containing a therapeutically effective amount of a compound of formula I, an enantiomer or a racemate or a salt thereof can be administered by methods well known in the art. Thus, a compound of formula I or a salt thereof can be administered either singly or with other pharmaceutical agents, for example, antihistamines, mediator release inhibitors, methyl xanthines, beta agonists or antiasthmatic steroids such as prednisone and prednisolone, orally, parenterally, rectally or by inhalation, for example, in the form of an aerosol, micropulverized powder or nebulized solution. For oral administration they can be administered in the form of tablets, capsules, for example, in admixture with talc, starch, milk sugar or other inert ingredients, that is, pharmaceutically acceptable carriers, or in the form of aqueous solutions, suspensions, elixirs or aqueous alcoholic solutions, for example, in admixture with sugar or other sweetening agents, flavoring agents, colorants, thickeners and other conventional pharmaceutical excipients. For parenteral administration, they can be administered as solutions or suspension, for example, as an aqueous or peanut oil solution or suspension using excipients and carriers conventional for this mode of administration. For administration as aerosols, they can be dissolved in a suitable pharmaceutically acceptable solvent, for example, ethyl alcohol or combinations of miscible solvents and mixed with a pharmaceutically acceptable propellant. Such aerosol compositions are packaged for use in pressurized container fitted with an aerosol valve suitable for release of the pressurized composition. Preferably, the aerosol valve is a metered valve, that is one which on activation releases a predetermined effective dose of the aerosol composition.

45

It is to be understood that formula I as used herein includes geometric isomers when Y and/or Z are -CH=CH-. The geometric isomers can be separated into the respective E- and Z-isomers utilizing known procedures as further exemplified herein.

50

Furthermore, since compounds of formula I of the invention may possess an asymmetric carbon atom they are ordinarily obtained as racemic mixtures. It is to be understood the enantiomers and diastereomers also form part of this invention. The resolution of such racemates into the optically active isomers can be carried out by known procedures. Some racemic mixtures can be precipitated as eutectics and can thereafter be separated. Chemical resolution is, however, preferred. By this method diastereomers are formed from the racemic mixture of a compound of formula I with an optically active resolving agent. The formed diastereomers are separated by selective crystallization or chromatography and converted to the corresponding optical isomer. Thus, the invention covers the racemates of the compounds of formula I as well as their optically active isomers (enantiomers).

55



In the following examples, the "usual work-up" procedure involves three extractions with the specified solvent. The organic extracts were combined, washed with water and saturated brine, dried over anhydrous magnesium sulfate, filtered and concentrated under water aspirator pressure. The residue was dried to constant weight at 45 ° C/high vacuum. All reactions except hydrogenations were carried out under an inert atmosphere of nitrogen or argon. All temperatures are given in degrees Celsius.

### EXAMPLE 1

#### Preparation of 7-(Phenylmethoxy)-8-propyl-4H-1-benzopyran-4-one

A mixture of 3.09 g (10.88 mmol) of 1-[2-hydroxy-4-(phenylmethoxy)-3-propylphenyl]ethanone, 1.55 g (13 mmol) of dimethylformamide dimethyl acetal and 2.7 ml of xylene was stirred and heated in a 120-130 ° oil-bath as methanol was distilled out using a Vigreux column over a 2 hr period. The bath temperature was then raised to 150-160 ° and the reaction mixture was stirred at this temperature for an additional 30 min. The mixture was cooled and concentrated at 60 °/high vacuum. To the viscous, red-brown, oily residue were added 2.48 g (13 mmol) of p-toluenesulfonic acid mono-hydrate and 25 ml of ethanol. The resulting solution was stirred and refluxed for 1.5 hr, then cooled and diluted with 100 ml of water. Work-up with ether in the usual manner gave a crude product which was purified by flash chromatography on silica gel eluting with 1:1 hexane-ether. There were obtained 2.8 g (87.5%) of 7-(phenylmethoxy)-8-propyl-4H-1-benzopyran-4-one as a beige solid. An analytical specimen was obtained from another experiment by recrystallization from ethyl acetate-hexane as a colorless solid, mp 87.5-89 °.

Anal. Calcd. for  $C_{19}H_{18}O_3$ : C, 77.53; H, 6.16. Found: C, 77.34; H, 6.06 %.

### EXAMPLE 2

#### Preparation of 2,3-Dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one

A mixture of 3.99 g (13.57 mmol) of 7-(phenylmethoxy)-8-propyl-4H-1-benzopyran-4-one, 0.8 g of 10% palladium on carbon and 300 ml of 1:1 methanol-ethyl acetate was stirred in an atmosphere of hydrogen. The progress of the hydrogenation was monitored by TLC. The mixture was filtered with suction through a Celite pad and the filter cake was washed with ethyl acetate. Concentration of the combined filtrate and washes in vacuo gave 2.78 g of a beige solid. Flash chromatography on silica gel eluting with 1:1 hexane-ether afforded 1.7 g (60.8%) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one. A sample was recrystallized from hexane-ethyl acetate giving a colorless solid, mp 126-129 °.

Anal. Calcd. for  $C_{12}H_{14}O_3$ : C, 69.89; H, 6.84. Found: C, 69.69; H, 6.92 %.

### EXAMPLE 3

#### Preparation of 2-[(5-Bromopentyl)oxy]benzenepropanoic acid methyl ester

A mixture of 3.6 g (20 mmol) of 2-hydroxybenzenepropanoic acid methyl ester, 22 ml (160 mmol) of 1,5-dibromopentane, 8.73 g (63.3 mmol) of anhydrous granular potassium carbonate and 145 ml of acetonitrile was stirred and refluxed for 24 hr. The resulting slurry was cooled and diluted with 300 ml of ether. The solids were removed by suction filtration and the filter cake was washed well with ether. The filtrate and washes were combined and concentrated in vacuo giving 38.59 g of a brown oil which was chromatographed on 200 g of silica gel eluting with 49:1 and 19:1 hexane-ether. The fractions containing the desired product were combined and concentrated giving 5.86 g of an oil which was dissolved in 50 ml of methanol containing 0.2 g of p-toluenesulfonic acid monohydrate. The solution was stirred at room temperature for 17 hr and refluxed for 5 hr before being cooled and concentrated in vacuo. The residue was dissolved in ether and the solution was washed with saturated sodium bicarbonate solution and worked-up in the usual manner. The oily residue was chromatographed on 100 g of silica gel. Elution with 19:1 hexane-ether afforded 4.85 g (73.7%) of 2-[(5-bromopentyl)oxy]benzene-propanoic acid methyl ester as a colorless oil.

**EXAMPLE 4****Preparation of 2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid**

5

A mixture of 0.43 g (2.1 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one, 0.66 g (2.0 mmol) of 2-[(5-bromopentyl)oxy]benzenepropanoic acid methyl ester, 1.0 g (7.25 mmol) of anhydrous granular potassium carbonate, 8.4 ml of anhydrous N,N-dimethylformamide and 16.8 ml of acetone was stirred and refluxed for 5 hr. The resulting slurry was filtered with suction and the solids were washed well with acetone. The filtrate and washes were concentrated in vacuo and the residue was dissolved in ether and worked-up in the usual manner giving 0.9 g of a yellow oil. This material was purified first by flash chromatography on silica gel eluting with 1:1 hexane-ether and then by conventional chromatography on 150 g of silica gel, eluting with 9:1 toluene-ethyl acetate giving 0.63 g (69.4%) of 2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid methyl ester as a viscous oil. This material was dissolved in 15 ml of tetrahydrofuran and 1.4 ml of 3N aqueous lithium hydroxide solution was added. The mixture was stirred at room temperature for 60 hr then diluted with water and extracted twice with ether (ether extracts discarded). The aqueous alkaline solution was acidified with 3N aqueous hydrochloric acid and worked-up with ether in the usual manner giving a viscous oil which crystallized. Recrystallization from hexane-ethyl acetate gave 0.32 g (52.4%) of 2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid as a colorless solid, mp 82-85 °.

20

Anal. Calcd. for  $C_{26}H_{32}O_6$ : C, 70.89; H, 7.32. Found: C, 70.65; H, 7.28%.

**EXAMPLE 5****Preparation of 2-(5-Hydroxy-1-pentynyl)benzaldehyde**

25

Argon was bubbled through a stirred mixture of 11.1 g (60 mmol) of 2-bromobenzaldehyde, 6.5 g (77 mmol) of 4-pentyn-1-ol, 450 mg of anhydrous cuprous iodide and 240 ml of dry triethylamine and 840 mg of dichlorobis(triphenylphosphine) palladium (II) was added. The mixture was heated to 90 ° and stirred at this temperature for 3 hr during which time a dense precipitate and a black color developed. The reaction mixture was cooled and poured into a mixture of ice and 3N hydrochloric acid. Extractive work-up with dichloromethane was carried out in the usual manner giving 12.7 g of a red-brown oil. This material was purified by flash chromatography on silica gel eluting with 2:1 hexane-ethyl acetate. There was obtained 5.4 g (48%) of 2-(5-hydroxy-1-pentynyl)benzaldehyde as an oil.

35

**EXAMPLE 6****Preparation of 2-(5-Hydroxypentyl)benzenepropanoic acid methyl ester**

40

A mixture of 2.4 g (12.7 mmol) of 2-(5-hydroxy-1-pentynyl)benzaldehyde, 5.0 g (15 mmol) of methyl (triphenylphosphoranylidene)acetate and 200 ml of toluene was stirred and refluxed for 4 hr and then kept overnight at room temperature. The resulting solution was concentrated in vacuo. The residue (9.2 g) was combined with 9.9 g of similarly prepared crude material from a separate experiment and flash chromatographed on silica gel eluting with 2:1 toluene-ethyl acetate. There was obtained 4.9 g of a pale-yellow oil. This material was dissolved in 200 ml of methanol and the solution was treated with 1 g of 10% palladium on carbon. The mixture was then stirred in an atmosphere of hydrogen at room temperature for 5.5 hr during which time the theoretical volume of hydrogen was absorbed. The catalyst was removed by suction filtration and the filtrate was concentrated in vacuo giving 4.87 g (75.8%) of 2-(5-hydroxypentyl)benzenepropanoic acid methyl ester as a colorless oil.

50

**EXAMPLE 7****Preparation of 2-(5-Iodopentyl)benzenepropanoic acid methyl ester**

55

A solution of 4.87 g (19.48 mmol) of 2-(5-hydroxypentyl)benzenepropanoic acid methyl ester from example 6, 4.15 ml of pyridine and 18 ml of chloroform was stirred with ice-bath cooling as 5.07 g (26.6 mmol) of p-toluenesulfonyl chloride was added in one portion. The mixture was stirred at 0-5 ° for 1 hr and then kept at this temperature overnight before being poured into saturated sodium bicarbonate solution.

Work-up with dichloromethane in the usual manner gave a colorless oily tosylate which was treated with 4.5 g (30 mmol) of sodium iodide and 50 ml of acetone. The resulting mixture was stirred at room temperature for 2 hr, kept at 0-5 ° overnight and, finally, refluxed for 5 hr after the addition of 100 ml of acetone. The mixture was poured into water and worked-up with ether in the usual manner (the ether solution was additionally washed with aqueous sodium thiosulfate solution) giving a yellow oil. Flash chromatography on silica gel eluting with 10:1 hexane-ethyl acetate afforded 5.75 g (82%) of 2-(5-iodopentyl) benzenepropanoic acid methyl ester as a colorless oil.

#### EXAMPLE 8

##### Preparation of 2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]benzenepropanoic acid

Using the procedure of example 4, 2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]-benzenepropanoic acid methyl ester was prepared in 67.5% yield starting from 0.35 g (1.69 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.54 g (1.5 mmol) of 2-(5-iodopentyl)-benzenepropanoic acid methyl ester. A 0.5 g (1.14 mmol) sample of this ester was treated with 20 ml of methanol and 3 ml of aqueous 1N sodium hydroxide solution. The mixture was stirred and refluxed for 2.5 hr and then the solvent was removed in vacuo. The residue was diluted with water, acidified and worked-up with ether in the usual manner. The product was recrystallized from hexane-ethyl acetate giving 2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]benzenepropanoic acid as a colorless solid, mp 94-96 °, in 58.2% overall yield.

Anal. Calcd. for  $C_{26}H_{32}O_5$ : C, 73.56; H, 7.60. Found: C, 73.21; H, 7.66%.

#### EXAMPLE 9

##### Preparation of 6-Hydroxy-5-propyl-1,2,3,4-tetrahydronaphthalen-1-one

A 1.78 g (8.81 mmol) sample of 6-(2-propenyloxy)-1,2,3,4-tetrahydronaphthalen-1-one was heated at 180-195 ° for 1.5 hr and at 215 ° for 1.5 hr. The resulting dark-brown oil was cooled and dissolved in warm ethyl acetate. The warm solution was treated with Norit-A and the mixture was filtered with suction through a Celite pad. The filter cake was washed well with ethyl acetate and then the filtrate and washes were combined and concentrated under reduced pressure. The residue was dried at 45 °/high vacuum giving 1.6 g of a tan solid which by TLC and NMR analysis was a mixture of 5- and 7-allyl isomers. This material was recrystallized twice from ethyl acetate giving 0.9 g (50.5%) of the pure desired 5-allyl isomer, mp 147-149 °. This material was dissolved in 45 ml of ethanol and treated with 0.1 g of 10% palladium on carbon. The mixture was stirred in an atmosphere of hydrogen at room temperature for 25 min during which time one equivalent of hydrogen gas was absorbed. The catalyst was removed by suction filtration over Celite and the filtrate was concentrated in vacuo giving 0.9 g (ca. 100%) of 6-hydroxy-5-propyl-1,2,3,4-tetrahydronaphthalen-1-one as an off-white solid, mp 159-160 °.

Anal. Calcd. for  $C_{13}H_{16}O_2$ : C, 76.44; H, 7.90. Found: C, 76.13; H, 7.83%.

#### EXAMPLE 10

##### Preparation of 2-[[5-(5-Oxo-1-propyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]pentyloxy]benzenepropanoic acid

Using the procedure of example 4, 2-[[5-(5-oxo-1-propyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]pentyloxy]benzenepropanoic acid methyl ester, an oil, was prepared in 80.7% yield starting from 0.38 g (1.86 mmol) of 6-hydroxy-5-propyl-1,2,3,4-tetrahydronaphthalen-1-one and 0.66 g (2.0 mmol) of 2-(5-bromopentyloxy)benzenepropanoic acid methyl ester. Saponification of this ester using the procedure of example 4 gave 2-[[5-(5-oxo-1-propyl-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]pentyloxy]benzenepropanoic acid in 77% yield as a colorless solid, mp 90-92 °, after recrystallization from hexane-ethyl acetate.

Anal. Calcd. for  $C_{27}H_{34}O_5$ : C, 73.95; H, 7.81. Found: C, 73.89; H, 7.92%.

**EXAMPLE 11****Preparation of rac-6-Acetyl-7-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid**

5 A mixture of 0.8 g (3.88 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one, 1.6 g (3.88 mmol) of rac-6-acetyl-7-[5-[(methylsulfonyl)oxy]pentyloxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid methyl ester, 0.78 g (5.65 mmol) of anhydrous potassium carbonate, 0.082 g of tris[2-(2-methoxyethoxy)-ethyl]amine (TDA-1), and 20 ml of toluene was stirred and refluxed for 6 hr. After being cooled, the reaction  
 10 mixture was diluted with ether and toluene and filtered with suction. The solids were washed with more toluene and ether and then the filtrate and washes were combined and concentrated in vacuo. The residue was dissolved in 1:1 ether-dichloromethane and washed with water and brine. Completion of the usual work-up afforded a solid residue which was purified by flash chromatography eluting with 1:1 hexane-ethyl acetate. There was obtained 1.85 g (91%) of rac-6-acetyl-7-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid methyl ester as a solid, mp 131-133 °. This material was saponified using the procedure described in example 8 giving rac-6-acetyl-7-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid as an off-white solid, mp 148-151 °, in 38.4% yield after recrystallization from hexane-ethyl acetate.  
 20 Anal. Calcd. for C<sub>29</sub>H<sub>34</sub>O<sub>8</sub>: C, 68.22; H, 6.71. Found: C, 67.87; H, 6.92%.

**EXAMPLE 12****Preparation of [2-[(5-Bromopentyl)oxy]phenoxy]acetic acid methyl ester**

25 A mixture of 2.6 g (10 mmol) of 2-[(5-bromopentyl)oxy]phenol, 1.8 g (12 mmol) of methyl bromoacetate, 4.4 g (32 mmol) of anhydrous granular potassium carbonate and 60 ml of dry acetonitrile was stirred and refluxed for 20 hr. The mixture was cooled and filtered with suction. The solids were washed with ether and the filtrate and washes were combined and concentrated in vacuo. The oily residue was purified by flash  
 30 chromatography on silica gel eluting with 3:1 hexane-ether. There was obtained 2.2 g (66.5%) of [2-[(5-bromopentyl)oxy]phenoxy]acetic acid methyl ester as an oil.

**EXAMPLE 13****35 Preparation of [2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]phenoxy]acetic acid**

Using the procedure of example 4, [2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]phenoxy]acetic acid was prepared in 72.3% overall yield starting from 0.31 g (1.5 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.53 g (1.6 mmol) of [2-[(5-bromopentyl)oxy]phenoxy]acetic acid methyl ester as a colorless solid, mp 98-99 °, recrystallized from hexane-ethyl acetate.  
 40 Anal. Calcd. for C<sub>25</sub>H<sub>30</sub>O<sub>7</sub>: C, 67.86; H, 6.83. Found: C, 67.90; H, 6.87%.

**EXAMPLE 14****45 Preparation of 2-[(5-Bromopentyl)oxy]-5-chlorobenzaldehyde**

A mixture of 7.82 g (50 mmol) of 5-chlorosalicylaldehyde, 92.1 g (0.4 mol) of 1,5-dibromopentane, 22.1 g (0.15 mol) of anhydrous granular potassium carbonate and 360 ml of acetonitrile was stirred and refluxed  
 50 for 20 hr. The resulting slurry was cooled and diluted with 300 ml of ether. The solids were removed by suction filtration and washed thoroughly with ether. The filtrate and washes were combined and concentrated under water aspirator pressure. The excess 1,5-dibromopentane was removed by distillation under high vacuum. Flash chromatography of the residue on silica gel eluting with 4:1 hexane-ether afforded 12.5 g (81.8%) of 2-[(5-bromopentyl)oxy]-5-chlorobenzaldehyde as a yellow oil.

55

**EXAMPLE 15****Preparation of (E/Z)-3-[2-[(5-Bromopentyl)oxy]-5-chlorophenyl]-2-propenoic acid methyl ester**

5 A mixture of 2 g (6.54 mmol) of 2-[(5-bromopentyl)oxy]-5-chlorobenzaldehyde, 2.4 g (7.17 mmol) of methyl (triphenylphosphoranylidene)acetate and 100 ml of toluene was stirred and refluxed for 4 hr and then stirred overnight at room temperature. The mixture was filtered with suction and the filtrate was concentrated in vacuo. The oily residue was triturated with hexane leading to the formation of a slurry which was filtered with suction. The solid (triphenylphosphine oxide) was washed thoroughly with hexane. The  
 10 filtrate and washes were combined and concentrated in vacuo giving 2.57 g of a yellow oil which was chromatographed on 50 g of silica gel. Elution with 9:1 hexane-ether afforded 2.02 g (85.4%) of (E/Z)-3-[2-[(5-bromopentyl)oxy]-5-chlorophenyl]-2-propenoic acid methyl ester as a colorless oil.

**EXAMPLE 16**

15

**Preparation of 2-[(5-Bromopentyl)oxy]-5-chlorobenzenepropanoic acid methyl ester**

A mixture of 2.02 g (5.59 mmol) of 3-[2-[(5-bromopentyl)oxy]-5-chlorophenyl]-2-propenoic acid methyl ester (mixture of E/Z-isomers), 90 ml of tetrahydrofuran, 190 ml of toluene and 1.26 g of 5% rhodium on alumina was stirred at room temperature in an atmosphere of hydrogen until reduction was complete. The  
 20 catalyst was removed by suction filtration and the filtrate was concentrated in vacuo giving 2.05 g (ca. 100%) of 2-[(5-bromopentyl)oxy]-5-chlorobenzenepropanoic acid methyl ester as a pale-yellow oil which was used without further purification

**EXAMPLE 17****Preparation of 5-Chloro-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid**

30 Using the procedure of example 4, 5-chloro-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid methyl ester, a pale-yellow oil, was prepared in quantitative yield starting from 0.62 g (3 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 1.21 g (3.33 mmol) of 2-[(5-bromopentyl)oxy]-5-chlorobenzenepropanoic acid methyl ester. Saponification using the procedure of example 4 afforded 1.01 g (71%) of 5-chloro-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid as a colorless solid, mp 101-103 °.  
 35

Anal. Calcd. for  $C_{26}H_{31}ClO_6$ : C, 65.75; H, 6.58; Cl, 7.46. Found: C, 65.91; H, 6.61; Cl, 7.44 %.

**EXAMPLE 18****Preparation of 7-[(5-Bromopentyl)oxy]-2,3-dihydro-8-propyl-4H-1-benzopyran-4-one**

A mixture of 0.413 g (2.00 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one, 3.0 g (13.05 mmol) of 1,5-dibromopentane, 1.4 g (10.13 mmol) of anhydrous granular potassium carbonate and 31 ml of 2-butanone was stirred and refluxed for 18 hr. The resulting slurry was filtered with suction and the  
 45 solids were washed thoroughly with ethyl acetate. The filtrate and washes were combined and concentrated in vacuo and the residue was purified by flash chromatography on 75 g of silica gel, eluting with 4:1 hexane-ethyl acetate giving 0.627 g (88%) of the title compound as a white solid, mp 47-48 °.

Anal. Calcd. for  $C_{17}H_{23}BrO_3$ : C, 57.47; H, 6.53; Br, 22.49. Found: C, 57.24; H, 6.49; Br, 22.69 %.

**EXAMPLE 19****Preparation of 7-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-2-benzofuran-carboxylic acid**

55 A mixture of 0.556 g (1.57 mmol) of 7-[(5-bromopentyl)oxy]-2,3-dihydro-8-propyl-4H-1-benzopyran-4-one, 0.323 g (1.57 mmol) of 7-hydroxy-2-benzofuran-carboxylic acid ethyl ester, 0.866 g (6.26 mmol) of anhydrous granular potassium carbonate and 16 ml of 2-butanone was stirred and refluxed for 16.5 hr. The resulting slurry was filtered with suction and the solids were washed thoroughly with ethyl acetate. The

filtrate and washes were combined and concentrated in vacuo and the residue was purified by flash chromatography on 70 g of silica gel eluting with 4:1 hexane-ethyl acetate giving 0.527 g (70%) of 7-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-2-benzofurancarboxylic acid ethyl ester as a white solid, mp 79.5-81 °. A mixture of 0.262 g (0.55 mmol) of this ester in 3.5 ml of tetrahydrofuran and 3.5 ml of water was treated with 35.1 mg (0.84 mmol) of lithium hydroxide monohydrate and the mixture was stirred for 17.5 hr. After being acidified with 16 ml of 3N aqueous sulfuric acid the resulting mixture was worked-up with ether and ethyl acetate in the usual manner. The crude product was recrystallized from hexane-ethyl acetate to give 0.185 g (74.9%) of the title compound as a white solid, mp 152-153.5 °.

Anal. Calcd. for  $C_{26}H_{28}O_7$ : C, 69.01; H, 6.24. Found: C, 68.84; H, 6.39 %.

#### EXAMPLE 20

##### Preparation of 5-[(3-Carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid

Starting with 0.275 g (0.78 mmol) of 7-[(5-bromopentyl)oxy]-2,3-dihydro-8-propyl-4H-1-benzopyran-4-one and 0.286 g (0.77 mmol) of 5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester, 5-[(3-carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid (0.163 g; 52% overall yield) was obtained as a white solid, mp 122-128 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 19.

Anal. Calcd. for  $C_{34}H_{36}O_9$ : C, 69.37; H, 6.17. Found: C, 69.86; H, 6.58 %.

#### EXAMPLE 21

##### Preparation of 2-[(6-Bromohexyl)oxy]-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester

A mixture of 0.393 g (1.06 mmol) of 5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester, 2.06 g (8.44 mmol) of 1,6-dibromohexane, 0.882 g (6.39 mmol) of anhydrous granular potassium carbonate and 15 ml of 2-butanone was stirred and refluxed for 18.5 hr. The resulting slurry was filtered with suction and the solids were washed thoroughly with ethyl acetate. The filtrate and washes were combined and concentrated in vacuo and the residue was purified by flash chromatography on 75 g of silica gel eluting with 5:1 hexane-ethyl acetate giving 0.43 g (75.8%) of the title compound as a colorless oil.

Anal. Calcd. for  $C_{27}H_{33}BrO_6$ : C, 60.79; H, 6.24; Br, 14.98. Found: C, 60.41; H, 6.27; Br, 15.30 %.

#### EXAMPLE 22

##### Preparation of 5-[(3-Carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyloxy]benzenepropanoic acid

A mixture of 0.144 g (0.70 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one, 0.371 g (0.70 mmol) of 2-[(6-bromohexyl)oxy]-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester, 0.479 g (3.47 mmol) of anhydrous granular potassium carbonate and 13.1 ml of 2-butanone was stirred and refluxed for 18 hr. The resulting slurry was filtered with suction and the solids washed thoroughly with ethyl acetate. The filtrate and washes were combined and concentrated in vacuo and the residue was purified by flash chromatography on 75 g of silica gel eluting with 3:1 hexane-ethyl acetate giving 0.37 g (80.6%) of 2-[6-[(2,3-dihydro-4-oxo-8-propyl-4H-1-benzopyran-7-yl)oxy]hexyloxy]-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester as a white solid, mp 58-59.5 °. A mixture of 0.331 g (0.50 mmol) of this ester in 6 ml of tetrahydrofuran and 6 ml of water was treated with 64.7 mg (1.54 mmol) of lithium hydroxide monohydrate and the resulting mixture was stirred for 25.5 hr at room temperature before being acidified with 17 ml of 3N aqueous sulfuric acid. Work-up with ethyl acetate in the usual manner gave a crude product which was recrystallized from hexane-ethyl acetate affording 0.242 g (79.7%) of the title compound as a white solid, mp 169-172 °.

Anal. Calcd. for  $C_{35}H_{38}O_9$ : C, 69.75; H, 6.36. Found: C, 69.57; H, 6.36 %.

**EXAMPLE 23****Preparation of 2-(4-Bromobutoxy)-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester**

Starting with 0.388 g (1.05 mmol) of 5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester and 1.81 g (8.38 mmol) of 1,4-dibromobutane, the title compound was obtained as a colorless oil in 81.2% yield using the procedure of example 21.

Anal. Calcd. for  $C_{25}H_{29}BrO_6$ : C, 59.41; H, 5.78; Br, 15.81. Found: C, 59.19; H, 5.75; Br, 15.51 %.

**EXAMPLE 24****Preparation of 5-[(3-Carboxyphenyl)carbonyl]-2-[4-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]butoxy]benzenepropanoic acid**

Starting with 0.144 g (0.70 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.35 g (0.69 mmol) of 2-(4-bromobutoxy)-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester, the title compound (0.202 g; 63.4% overall yield) was obtained as a white solid, mp 177-180 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 22.

Anal. Calcd. for  $C_{33}H_{34}O_9$ : C, 68.98; H, 5.96. Found: C, 68.98; H, 6.06 %.

**EXAMPLE 25****Preparation of 5-[(5-Bromopentyl)oxy]-2-benzofurancarboxylic acid ethyl ester**

Starting with 2.41 g (11.69 mmol) of 5-hydroxy-2-benzofurancarboxylic acid ethyl ester and 8.06 g (35.06 mmol) of 1,5-dibromopentane, the title compound (3.03 g; 73%) was obtained as a white solid, mp 31 °, using the procedure of example 21.

Anal. Calcd. for  $C_{16}H_{19}BrO_4$ : C, 54.10; H, 5.39; Br, 22.50. Found: C, 54.03; H, 5.28; Br, 22.36 %.

**EXAMPLE 26****Preparation of 5-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-2-benzofurancarboxylic acid**

Starting with 0.207 g (1.00 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.355 g (1.00 mmol) of 5-[(5-bromopentyl)oxy]-2-benzofurancarboxylic acid ethyl ester, there was obtained 0.093 g (20.5%) of the title compound as an off-white solid, mp 192-195 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 22.

Anal. Calcd. for  $C_{26}H_{28}O_7$ : C, 69.01; H, 6.24. Found: C, 68.63; H, 6.25 %.

**EXAMPLE 27****Preparation of 2-[[5-(Acetyloxy)pentyl]oxy]benzaldehyde**

A mixture of 12.2 g (0.1 mol) of salicylaldehyde, 23 g (0.11 mol) of 5-bromopentyl acetate, 44.2 g (0.3 mol) of anhydrous granular potassium carbonate and 700 ml of acetonitrile was stirred and refluxed for 20 hr. After being cooled, the resulting mixture was filtered with suction and the solids were washed well with ether. The filtrate and washes were combined and concentrated in vacuo giving a yellow oil which was purified by flash chromatography on silica gel eluting with 4:1 hexane-ether. There was obtained 10.9 g (43.6%) of 2-[[5-(acetyloxy)pentyl]oxy]benzaldehyde as an oil.

**EXAMPLE 28****Preparation of (E/Z)-3-[2-[[5-(Acetyloxy)pentyl]oxy]phenyl]-2-propenoic acid methyl ester**

A mixture of 3.75 g (15 mmol) of 2-[[5-(acetyloxy)pentyl]oxy]benzaldehyde, 6.02 g (18 mmol) of methyl (triphenylphosphoranylidene)acetate and 200 ml of toluene was stirred and refluxed for 4 hr and then stirred

overnight at room temperature. The solvent was removed under reduced pressure and the oily residue was flash chromatographed on silica gel eluting with 2:1 hexane-ether. There was obtained 4.4 g (96%) of (E/Z)-3-[2-[[5-(acetyloxy)pentyl]oxy]phenyl]-2-propenoic acid methyl ester as an oil.

#### 5 **EXAMPLE 29**

##### **Preparation of 2-[[5-(Acetyloxy)pentyl]oxy]benzenepropanoic acid methyl ester**

10 A mixture of 4.4 g of (E/Z)-3-[2-[[5-(acetyloxy)pentyl]oxy]phenyl]-2-propenoic acid methyl ester and 0.5 g of 10% palladium on carbon in 200 ml of ethyl acetate was stirred in an atmosphere of hydrogen until hydrogen uptake ceased. The catalyst was removed by suction filtration and the filtrate was concentrated in vacuo giving 4.3 g (97%) of 2-[[5-(acetyloxy)pentyl]oxy]benzenepropanoic acid methyl ester as a colorless oil.

#### 15 **EXAMPLE 30**

##### **Preparation of 2-[[5-(Acetyloxy)pentyl]oxy]-5-acetylbenzenepropanoic acid methyl ester**

20 A solution of 4.3 g (13.96 mmol) of 2-[[5-(acetyloxy)pentyl]oxy]benzenepropanoic acid methyl ester and 2.18 g (27.8 mmol) of freshly distilled acetyl chloride in 250 ml of dry dichloromethane was stirred with ice-bath cooling while 7.5 g (56.7 mmol) of anhydrous aluminum chloride was added in one portion. The resulting mixture was stirred at 0-5 ° for 2 hr before being treated with ice. Work-up with dichloromethane in the usual manner gave an oil which was chromatographed on 100 g of silica gel. Elution with 1:1 hexane-ether afforded 4.22 g (86.4%) of 2-[[5-(acetyloxy)pentyl]oxy]-5-acetylbenzenepropanoic acid methyl ester as an almost colorless oil.

#### **EXAMPLE 31**

##### **Preparation of 2-[(5-Hydroxypentyl)oxy]-5-acetylbenzenepropanoic acid methyl ester**

30 A solution of 4.22 g (12.06 mmol) of 2-[[5-(acetyloxy)pentyl]oxy]-5-acetylbenzenepropanoic acid methyl ester and 0.1 g of p-toluenesulfonic acid monohydrate in 50 ml of methanol was stirred and refluxed for 3.5 hr and stirred at room temperature for 21 hr. Most of the methanol was removed in vacuo and the residue was diluted with water and worked-up with ether in the usual manner (the combined ether extracts were additionally washed with saturated aqueous sodium bicarbonate). The product was purified by flash chromatography on silica gel eluting with 1:2 hexane-ethyl acetate. There was obtained 3.6 g (97%) of 2-[(5-hydroxypentyl)oxy]-5-acetylbenzenepropanoic acid methyl ester as a viscous oil.

#### **EXAMPLE 32**

##### **Preparation of 2-[[5-[(Methylsulfonyl)oxy]pentyl]oxy]-5-acetylbenzenepropanoic acid methyl ester**

40 A solution of 0.62 g (2 mmol) of 2-[(5-hydroxypentyl)oxy]-5-acetylbenzenepropanoic acid methyl ester and 2 ml of triethylamine in 6 ml of ethyl acetate was stirred with ice-bath cooling while 0.6 ml of methanesulfonyl chloride was added dropwise. The resulting mixture was stirred at 0-5 ° for 1.33 hr and then poured into ice-3N hydrochloric acid. Work-up with ethyl acetate in the usual manner gave 0.96 g of 2-[[5-[(methylsulfonyl)oxy]pentyl]oxy]-5-acetylbenzenepropanoic acid methyl ester as an oil which was used without further purification.

#### 50 **EXAMPLE 33**

##### **Preparation of 5-Acetyl-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid**

55 Using the procedure of example 11 and starting with 0.2 g (1 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.39 g (1 mmol) of 2-[[5-[(methylsulfonyl)oxy]pentyl]oxy]-5-acetylbenzenepropanoic acid methyl ester, 5-acetyl-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid was obtained in 64.3% overall yield as a colorless solid, mp 115-118 °



(recrystallized from hexane-ethyl acetate).

Anal. Calcd. for  $C_{28}H_{34}O_7$ : C, 69.69; H, 7.10. Found: C, 69.47; H, 7.22 %.

#### EXAMPLE 34

##### Preparation of 2-(6-Hydroxy-1-hexynyl)benzaldehyde

Using the procedure of example 5 and starting with 11.1 g (60 mmol) of 2-bromobenzaldehyde and 7.62 g (77 mol) of 5-hexyn-1-ol, 2-(6-hydroxy-1-hexynyl)benzaldehyde was obtained in 59.4% yield as a yellow oil.

#### EXAMPLE 35

##### Preparation of 2-(6-Hydroxyhexyl)benzenepropanoic acid methyl ester

Using the procedure of example 6, 7.2 g (35.6 mmol) of 2-(6-hydroxy-1-hexynyl)benzaldehyde was converted in 78% overall yield into 2-(6-hydroxyhexyl)benzenepropanoic acid methyl ester as a colorless oil.

#### EXAMPLE 36

##### Preparation of 2-[6-[(Methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester

Using the procedure of example 32, 2-(6-hydroxyhexyl)benzenepropanoic acid methyl ester (2 mmol) was converted into 2-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester, a yellow oil, in quantitative yield.

#### EXAMPLE 37

##### Preparation of 2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid

Using the procedure of example 11 and starting with 0.2 g (1 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.32 g (1 mmol) of 2-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester, 2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid was obtained in 45.6% overall yield as a colorless solid, mp 98-99 ° (recrystallized from hexane-ethyl acetate).

Anal. Calcd. for  $C_{27}H_{34}O_5$ : C, 73.95; H, 7.81. Found: C, 73.89; H, 7.89 %.

#### EXAMPLE 38

##### Preparation of 2-[3-(Chloromethyl)phenylmethoxy]benzenepropanoic acid methyl ester

A mixture of 1.8 g (10 mmol) of 2-hydroxybenzenepropanoic acid methyl ester, 14 g (80 mmol) of  $\alpha, \alpha'$ -dichloro-m-xylene, 4.25 g (30.8 mmol) of anhydrous granular potassium carbonate and 70 ml of acetonitrile was stirred and refluxed for 4 hr. After being cooled, the resulting mixture was diluted with 200 ml of ether and filtered with suction. The solids were washed thoroughly with ether and then the filtrate and washes were combined and concentrated in vacuo. The oily residue was chromatographed on 100 g of silica gel. Elution with 19:1 hexane-ether afforded 1.74 g (54.6%) of 2-[3-(chloromethyl)phenylmethoxy]benzenepropanoic acid methyl ester as a colorless oil.

#### EXAMPLE 39

##### Preparation of 2-[3-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]methyl]phenylmethoxy]benzenepropanoic acid

Using the procedure of example 4 and starting with 0.62 g (3 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 1.05 g (3.3 mmol) of 2-[3-(chloromethyl)phenylmethoxy]benzenepropanoic acid methyl ester, 2-[3-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]methyl]phenylmethoxy]-

benzenepropanoic acid was prepared in 52% overall yield as an off-white solid, mp 132-135 ° (recrystallized from acetonitrile).

Anal. Calcd. for  $C_{29}H_{30}O_6$ : C, 73.40; H, 6.37. Found: C, 73.19; H, 6.31 %.

#### 5 **EXAMPLE 40**

##### **Preparation of 2-[5-[(2,3-Dihydro-3-oxo-7-propylbenzofuran-6-yl)oxy]pentyloxy]benzenepropanoic acid**

10 A mixture of 0.154 g (0.8 mmol) of 6-hydroxy-7-propyl-2H-benzofuran-3-one, 0.27 g (0.82 mmol) of 2-[(5-bromopentyl)oxy]benzenepropanoic acid methyl ester, 0.382 g (2.77 mmol) of anhydrous granular potassium carbonate and 6 ml of anhydrous N,N-dimethylformamide was stirred at 60-65 ° for 3 hr. The resulting slurry was cooled and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with 7:3 and 6:4 hexane-ethyl acetate. There was obtained 0.24 g (68%)  
 15 of 2-[5-[(2,3-dihydro-3-oxo-7-propylbenzofuran-6-yl)oxy]pentyloxy]benzenepropanoic acid methyl ester as a pale-yellow oil. A 0.1 g (0.227 mmol) sample of this material was dissolved in 10 ml of tetrahydrofuran and 1 ml of 3N aqueous hydrochloric acid was added. The mixture was stirred at room temperature for 2.5 hr then heated at 60-65 ° for 28 hr. After being stirred overnight at room temperature, the solution was diluted with water and worked-up with dichloromethane in the usual manner giving a viscous oil. Flash chromatog-  
 20 raphy on silica gel eluting with ethyl acetate and 9:1 ethyl acetate-methanol gave 0.04 g (41.5%) of 2-[5-[(2,3-dihydro-3-oxo-7-propylbenzofuran-6-yl)oxy]pentyloxy]benzenepropanoic acid as a pale-yellow gum which crystallized. Trituration of a sample with ether-hexane gave a pale-yellow solid, mp 101-102.5 °.

#### **EXAMPLE 41**

25

##### **Preparation of 4-(3-Formyl-4-hydroxyphenoxy)butanoic acid ethyl ester**

A 1.86 g (46.4 mmol) sample of 60% sodium hydride-mineral oil dispersion was washed free of the oil with heptane and suspended in 100 ml of dimethyl sulfoxide. The slurry was stirred at room temperature  
 30 while a solution of 2.76 g (20 mmol) of 2,5-dihydroxybenzaldehyde in 10 ml of dimethyl sulfoxide was added dropwise over a 5 min period. The resulting mixture was stirred at room temperature for 45 min during which time hydrogen gas was evolved and a dark red-orange coloration developed. To the stirred mixture were added dropwise 4.3 g (22 mmol) of ethyl 4-bromobutyrate washed in with 5 ml of dimethyl sulfoxide. The reaction mixture was stirred at room temperature for 1.5 hr and at 70 ° for 18 hr. After being  
 35 cooled, the jet-black mixture was poured into 200 ml of cold 0.75N hydrochloric acid. Work-up with ether in the usual manner gave 3.84 g of a dark-brown oil which was chromatographed on 100 g of silica gel. Elution with 4:1 hexane-ether afforded 0.79 g (15.7%) of 4-(3-formyl-4-hydroxyphenoxy)butanoic acid ethyl ester as a yellow oil.

#### 40 **EXAMPLE 42**

##### **Preparation of 4-[[5-(Acetyloxy)pentyl]oxy]-3-formylphenoxy]butanoic acid ethyl ester**

A mixture of 4-(3-formyl-4-hydroxyphenoxy)butanoic acid ethyl ester from the preceding example (0.79 g; 3.13 mmol), 0.72 g (3.44 mmol) of 5-bromopentyl acetate, 1.37 g (9.93 mmol) of anhydrous granular potassium carbonate and 23 ml of acetonitrile was stirred and refluxed for 18 hr. The resulting tan slurry was cooled, diluted with 75 ml of ether and filtered with suction. The solids were washed thoroughly with ether. The filtrate and washes were combined and concentrated in vacuo giving 1.22 g of 4-[[5-(acetyloxy)-  
 45 pentyl]oxy]-3-formylphenoxy]butanoic acid ethyl ester as an amber oil which was used without further purification.  
 50

#### **EXAMPLE 43**

##### **Preparation of (E/Z)-4-[4-[[5-(Acetyloxy)pentyl]oxy]-3-(3-ethoxy-3-oxo-1-propenyl)phenoxy]butanoic acid ethyl ester**

55

A mixture of the crude 4-[[5-(acetyloxy)pentyl]oxy]-3-formylphenoxy]butanoic acid ethyl ester from the preceding example (1.22 g; ca. 3.13 mmol), 1.63 g (4.68 mmol) of (carbethoxymethylene)-

triphenylphosphorane and 10 ml of toluene was stirred and refluxed for 4.5 hr and then stirred overnight at room temperature. The solvent was removed under reduced pressure and the oily residue was triturated with 1:1 hexane-ether. The resulting solid was filtered with suction and washed with 1:1 hexane-ether. The filtrate and washes were combined and concentrated in vacuo giving 2.3 g of an oil which was flash chromatographed on silica gel eluting with 1:1 hexane-ether. There was obtained 1.1 g (78%) of (E/Z)-4-[4-[5-(acetyloxy)pentyl]oxy]-3-(3-ethoxy-3-oxo-1-propenyl)phenoxy]butanoic acid ethyl ester as a oil.

#### EXAMPLE 44

##### Preparation of 2-[[5-(Acetyloxy)pentyl]oxy]-5-(4-ethoxy-4-oxobutoxy)benzenepropanoic acid ethyl ester

A mixture of 1.1 g (2.4 mmol) of (E/Z)-4-[4-[5-(acetyloxy)pentyl]oxy]-3-(3-ethoxy-3-oxo-1-propenyl)-phenoxy]butanoic acid ethyl ester from the preceding example and 0.15g of 10% palladium on carbon in 50ml of ethyl acetate and 10 ml of ethanol was stirred in an atmosphere of hydrogen until hydrogen uptake ceased. The catalyst was removed by suction filtration and the filtrate was concentrated in vacuo giving 1.0 g (91%) of 2-[[5-(acetyloxy)pentyl]oxy]-5-(4-ethoxy-4-oxobutoxy)benzenepropanoic acid ethyl ester as a colorless oil.

#### EXAMPLE 45

##### Preparation of 2-[(5-Hydroxypentyl)oxy]-5-(4-ethoxy-4-oxobutoxy)benzenepropanoic acid ethyl ester

A solution of 1.0 g (2.2 mmol) of 2-[[5-(acetyloxy)pentyl]oxy]-5-(4-ethoxy-4-oxobutoxy)benzenepropanoic acid ethyl ester from the preceding example and 0.018 g of p-toluenesulfonic acid monohydrate in 10 ml of ethanol was stirred and refluxed for 30 hr and stirred at room temperature for 21 hr. Most of the ethanol was removed in vacuo and the residue was diluted with water and worked-up with ether in the usual manner (the combined ether extracts were additionally washed with saturated aqueous Sodium bicarbonate solution). The product was purified by flash chromatography on silica gel eluting with 1:1 hexane-ethyl acetate. There was obtained 0.6 g (66.5%) of 2-[(5-hydroxypentyl)oxy]-5-(4-ethoxy-4-oxobutoxy)benzenepropanoic acid ethyl ester as a viscous oil.

#### EXAMPLE 46

##### Preparation of 2-[[5-[(Methylsulfonyl)oxy]pentyl]oxy]-5-(4-ethoxy-4-oxobutoxy)benzenepropanoic acid ethyl ester

Using the procedure of example 32, the 2-[(5-hydroxypentyl)oxy]-5-(4-ethoxy-4-oxobutoxy)-benzenepropanoic acid ethyl ester from the preceding example (0.6 g; 1.46 mmol) was converted into 2-[[5-[(methylsulfonyl)oxy]pentyl]oxy]-5-(4-ethoxy-4-oxo-butoxy)benzenepropanoic acid ethyl ester in essentially quantitative yield and was used without further purification.

#### EXAMPLE 47

##### Preparation of 5-(3-Carboxypropoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepropanoic acid

Using the procedure of example 11 and starting with 0.28 g (1.4 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.7 g (1.4 mmol) of 2-[5-(methylsulfonyl)oxypentyl]oxy]-5-(3-ethoxycarbonylpropoxy)benzenepropanoic acid ethyl ester, 5-(3-ethoxycarbonylpropoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepropanoic acid ethyl ester was obtained in 83.6% yield (0.7 g) as a solid. This diester (1.17 mmol) was saponified with 3 ml of 3N aqueous lithium hydroxide solution in 25 ml of tetrahydrofuran at room temperature for 37 hr. Work-up as in example 4 gave a light-brown oily acid which was flash-chromatographed on silica gel eluting with 95:5:1 chloroform-methanol-acetic acid. There was obtained 0.39 g (61.5%) of pure 5-(3-carboxypropoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]benzenepropanoic acid. Recrystallization from hexaneethyl acetate gave a colorless solid, mp 119-124 °.

Anal. Calcd. for  $C_{30}H_{38}O_9$ : C, 66.40; H, 7.06. Found: C, 66.21; H, 7.10%.

**EXAMPLE 48****5 Preparation of 4-(4-Bromo-3-formylphenoxy)butanoic acid ethyl ester**

A mixture of 3.5 g (17.4 mmol) of 2-bromo-5-hydroxybenzaldehyde, 3.7 g (19 mmol) of ethyl 4-bromobutyrate, 5.5 g (40 mmol) of anhydrous granular potassium carbonate and 40 ml of dry dimethyl sulfoxide was stirred at room temperature for 5 hr and then kept at room temperature overnight. The  
10 resulting slurry was poured into ice-water and worked-up with ether in the usual manner giving an oily product which was flash-chromatographed on silica gel. Elution with 2:1 hexane-ether afforded 4.4 g (80.3%) of 4-(4-bromo-3-formylphenoxy)butanoic acid ethyl ester as an oil.

**EXAMPLE 49****15 Preparation of rac-4-[3-Formyl-4-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]butanoic acid ethyl ester**

Using the procedure of example 5 and starting with 3.15 g (10 mmol) of 4-(4-bromo-3-formylphenoxy)-  
20 butanoic acid ethyl ester and 2.34 g (12.8 mmol) of rac-6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexyne, rac-4-[3-formyl-4-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]butanoic acid ethyl ester was prepared in 93.7% yield as an oil.

**EXAMPLE 50****25 Preparation of rac-(E)-4-[3-(3-Methoxy-3-oxo-1-propenyl)-4-[6-(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]butanoic acid ethyl ester**

Using the procedure of example 28 and starting with 3.9 g (9.37 mmol) of rac-4-[3-formyl-4-[6-  
30 (tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]butanoic acid ethyl ester and 3.69 g (11 mmol) of methyl (triphenylphosphoranylidene)acetate, rac-(E)-4-[3-(3-methoxy-3-oxo-1-propenyl)-4-[6-(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]butanoic acid ethyl ester was prepared in 98% yield as an oil.

**EXAMPLE 51****35 Preparation of rac-2-[6-[(Tetrahydro-2H-pyran-2-yl)oxy]hexyl]-5-(4-ethoxy-4-oxobutoxy)-benzenepropanoic acid methyl ester**

A 4.3 g (9.1 mmol) sample of rac-(E)-4-[3-(3-methoxy-3-oxo-1-propenyl)-4-[6-(tetrahydro-2H-pyran-2-yl)-  
40 oxy]-1-hexynyl]phenoxy]butanoic acid ethyl ester was hydrogenated in 300 ml of methanol over 0.5 g of 10% palladium on carbon at room temperature and atmospheric pressure until hydrogen uptake ceased. The catalyst was filtered with suction and washed with ethyl acetate. Concentration of the combined filtrate and washes gave 4.26 g (97.8%) of rac-2-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]-5-(4-ethoxy-4-oxobutoxy)-  
45 benzenepropanoic acid methyl ester as an oil.

**EXAMPLE 52****Preparation of 2-(6-Hydroxyhexyl)-5-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester**

A solution of 4.26 g (8.91 mmol) of rac-2-[6-[(3,4,5,6-tetrahydro-2H-pyran-2-yl)oxy]hexyl]-5-(4-ethoxy-4-  
50 oxobutoxy)benzenepropanoic acid methyl ester, 0.16 g of p-toluenesulfonic acid monohydrate and 75 ml of methanol was stirred and refluxed for 24 hr. The solvent was removed in vacuo and the residue was dissolved in ether. The ether solution was washed with saturated sodium bicarbonate solution and processed in the usual manner giving an oil. This material was flash-chromatographed on silica gel eluting  
55 with 1:1 hexane-ethyl acetate. There was obtained 2.0 g (59%) of 2-(6-hydroxyhexyl)-5-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester as a colorless oil.

**EXAMPLE 53****Preparation of 2-[6-[(Methylsulfonyl)oxy]hexyl]-5-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester**

Using the procedure of example 32, 2-(6-hydroxyhexyl)-5-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester was converted into 2-[6-[(methylsulfonyl)oxy]hexyl]-5-(4-methoxy-4-oxobutoxy)-benzenepropanoic acid methyl ester, an oil, in essentially quantitative yield.

**EXAMPLE 54****Preparation of 5-(3-Carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid**

Using the procedure of example 11 and starting with 0.28 g (1.4 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.64 g (1.4 mmol) of 2-[6-[(methylsulfonyl)oxy]hexyl]-5-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester, 5-(4-methoxy-4-oxobutoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid methyl ester was obtained in 86.7% yield (0.69 g) as an oil. This diester (1.21 mmol) was saponified with 2 ml of 3N aqueous lithium hydroxide solution in 20 ml of tetrahydrofuran at room temperature for 24 hr. Work-up as in example 4 gave a light-brown oily acid which was flash-chromatographed on silica gel eluting with 95:5:1 chloroform-methanol-acetic acid. There was obtained 0.6 g (91.8%) of pure 5-(3-carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid. Recrystallization from hexane-ethyl acetate gave 0.49 g (75%) of a colorless solid, mp 119-120 °.

Anal. Calcd. for  $C_{31}H_{40}O_8$ : C, 68.87; H, 7.46. Found: C, 68.69; H, 7.30 %.

**EXAMPLE 55****Preparation of 5-(5-Ethoxy-5-oxopentyl)oxy)-2-hydroxybenzenepropanoic acid ethyl ester**

A mixture of 1.5 g (9.15 mmol) of 6-hydroxy-3,4-dihydrocoumarin, 2.1 g (10 mmol) of ethyl 5-bromovalerate, 4.16 g (30 mmol) of anhydrous granular potassium carbonate and 15 ml of N,N-dimethylformamide was stirred at room temperature for 23 hr. The resulting dark-brown slurry was diluted with ether and washed with water and brine. Completion of the usual work-up gave 2.32 g of a red-range oil which was chromatographed on 50 g of silica gel. Elution with 1:1 hexane-ether gave 2.03 g of a yellow oil which was a mixture of the desired 5-[(3,4-dihydro-2-oxo-2H-1-benzopyran-6-yl)oxy]pentanoic acid ethyl ester and an impurity. This material was dissolved in 25 ml of ethanol and 52 mg of p-toluenesulfonic acid monohydrate was added. The resulting solution was stirred and refluxed for 22.5 hr and then concentrated in vacuo. The residue was dissolved in ether and the ether solution was processed in the usual manner giving an amber oil. This material was chromatographed on 50 g of silica gel. Elution with 1:1 hexane-ether afforded 1.90 g (61.4%) of 5-(5-ethoxy-5-oxopentyl)oxy)-2-hydroxybenzenepropanoic acid ethyl ester as a pale-yellow oil.

**EXAMPLE 56****Preparation of 2-[(5-Hydroxypentyl)oxy]-5-(5-methoxy-5-oxopentyl)oxy)benzenepropanoic acid methyl ester**

A mixture of 1.9 g (5.62 mmol) of 5-(5-ethoxy-5-oxopentyl)oxy)-2-hydroxybenzenepropanoic acid ethyl ester from the preceding example, 1.29 g (6.18 mmol) of 5-bromopentyl acetate, 2.15 g (15.6 mmol) of anhydrous granular potassium carbonate and 15 ml of dimethyl sulfoxide was stirred at room temperature for 18.5 hr. The resulting slurry was diluted with ether and washed with water and brine. The ether solution was processed in the usual manner giving 2.64 g of a pale-yellow oil. This material was dissolved in 50 ml of methanol and 0.1 g of p-toluenesulfonic acid monohydrate was added. The solution was stirred and refluxed for 23 hr and then concentrated in vacuo. The residue was dissolved in ether and the ether solution was washed with saturated aqueous sodium bicarbonate solution before being processed in the usual manner to give 2.18 g of an oil. This material was chromatographed on 50 g of silica gel. Elution with 1:1 hexane-ethyl acetate afforded 1.46 g (65.6%) of 2-[(5-hydroxypentyl)oxy]-5-(5-methoxy-5-oxopentyl)oxy)benzenepropanoic acid methyl ester as an almost colorless oil.

**EXAMPLE 57****Preparation of 2-[[5-[(Methylsulfonyl)oxy]pentyl]oxy]-5-(5-methoxy-5-oxopentyl)oxy]-benzenepropanoic acid methyl ester**

Using the procedure of example 32, the 2-[(5-hydroxypentyl)oxy]-5-(5-methoxy-5-oxopentyl)oxy)-benzenepropanoic acid methyl ester from the preceding example (1.46 g; 3.7 mmol) was converted into 2-[[5-[(methylsulfonyl)oxy]pentyl]oxy]-5-(5-methoxy-5-oxopentyl)oxy)-benzenepropanoic acid methyl ester, an oil, in essentially quantitative yield.

**EXAMPLE 58****Preparation of 5-(4-Carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid hemihydrate**

Using the procedure of example 11 and starting with 0.28 g (1.4 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.66 g (1.4 mmol) of 2-[[5-[(methylsulfonyl)oxy]pentyl]oxy]-5-(5-methoxy-5-oxopentyl)oxy)-benzenepropanoic acid methyl ester, 5-(5-methoxy-5-oxopentyl)oxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid methyl ester was obtained in 61% yield (0.5 g) as a colorless solid. This diester (0.85 mmol) was saponified with 3 ml of 3N aqueous lithium hydroxide solution in 20 ml of tetrahydrofuran at room temperature for 24 hr. Work-up as in example 4 gave a crystalline acid which was flash-chromatographed on silica gel eluting with 95:5:1 chloroform-methanol-acetic acid. There was obtained 0.44 g (93%) of pure 5-(4-carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid. Recrystallization from ethyl acetate gave 0.35 g (74%) of a colorless solid, mp 138-139 °.

Anal. Calcd. for  $C_{31}H_{40}O_9 \cdot 0.5H_2O$ : C, 65.83; H, 7.13. Found: C, 66.19; H, 7.21 %.

**EXAMPLE 59****Preparation of 2-Hydroxy-6-[(5-hydroxypentyl)oxy]benzenepropanoic acid methyl ester**

A mixture of 1.17 g (7.13 mmol) of 5-hydroxy-3,4-dihydrocoumarin, 1.64 g (7.85 mmol) of 5-bromopentyl acetate, 2.72 g (19.74 mmol) of anhydrous granular potassium carbonate and 18 ml of dimethyl sulfoxide was stirred at room temperature for 18 hr. The resulting pink slurry was diluted with ether and washed three times with water and once with saturated brine. Completion of the usual work-up gave 0.76 g of a yellow oil. The aqueous washes were combined and acidified with 6N hydrochloric acid. Work-up with ether in the usual manner gave 1.43 g of a viscous red oil. These neutral and acidic products were combined, dissolved in 60 ml of methanol containing 0.11 g of p-toluenesulfonic acid and the solution was stirred and refluxed for 20.5 hr. Removal of the methanol under reduced pressure left an oil which was dissolved in ether. The ether solution was washed with dilute sodium bicarbonate solution and then processed in the usual manner giving a yellow oil. This material was purified by flash chromatography on silica gel eluting with 1:2 hexane-ethyl acetate. There was obtained 1.4 g (69.6%) of 2-hydroxy-6-[(5-hydroxy-pentyl)oxy]benzenepropanoic acid methyl ester as a yellow viscous oil.

**EXAMPLE 60****Preparation of 6-[(5-Hydroxypentyl)oxy]-2-(5-ethoxy-5-oxopentyl)oxy)benzenepropanoic acid methyl ester**

A mixture of the 2-hydroxy-6-[(5-hydroxypentyl)oxy]benzenepropanoic acid methyl ester from the preceding example (1.4 g; 4.96 mmol), 1.13 g (5.4 mmol) of ethyl 5-bromovalerate, 1.57 g (11.4 mmol) of anhydrous granular potassium carbonate and 12 ml of dimethyl sulfoxide was stirred at room temperature for 6 hr. The resulting slurry was filtered with suction and the solids were washed well with ethyl acetate. The filtrate and washes were combined and treated with water. Work-up with ether in the usual manner gave an oily product which was purified by chromatography on silica gel. Elution with 1:3 hexane-ether afforded 1.0 g (49.3%) of 6-[(5-hydroxypentyl)oxy]-2-(5-ethoxy-5-oxopentyl)oxy)benzenepropanoic acid methyl ester as an oil.

**EXAMPLE 61****Preparation of 6-(5-Ethoxy-5-oxopentyloxy)-2-[[5-[(methylsulfonyl)oxy]pentyloxy]benzenepropanoic acid methyl ester**

Using the procedure of example 32, the 6-[(5-hydroxypentyl)oxy]-2-(5-ethoxy-5-oxopentyloxy)-benzenepropanoic acid methyl ester from the preceding example (1.0 g; 2.43 mmol) was converted into 6-(5-ethoxy-5-oxopentyloxy)-2-[[5-[(methylsulfonyl)oxy]pentyloxy]benzenepropanoic acid methyl ester, an oil, in 84% yield.

**EXAMPLE 62****Preparation of 6-(4-Carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid**

Using the procedure of example 11 and starting with 0.2 g (1.0 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.49 g (1.0 mmol) of 6-(5-ethoxy-5-oxopentyloxy)-2-[[5-[(methylsulfonyl)oxy]pentyloxy]benzenepropanoic acid methyl ester, 6-(5-ethoxy-5-oxopentyloxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid methyl ester was obtained in 72% yield (0.43 g) as a colorless solid. This diester (0.72 mmol) was saponified with 2 ml of 3N aqueous lithium hydroxide solution in 20 ml of tetrahydrofuran at room temperature for 24 hr. Work-up as in example 4 gave a crystalline acid which was flash-chromatographed on silica gel eluting with 95:5:1 chloroform-methanol-acetic acid. There was obtained 0.35 g of pure 6-(4-carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid. Recrystallization from ethyl acetate-hexane gave 0.22 g (55%) of a colorless solid, mp 85-87 °.

Anal. Calcd. for  $C_{31}H_{40}O_9$ : C, 66.89; H, 7.24. Found: C, 67.06; H, 7.35 %.

**EXAMPLE 63****Preparation of 3-[[5-(Acetyloxy)pentyloxy]benzaldehyde**

A mixture of 1.22 g (10 mmol) of 3-hydroxybenzaldehyde, 2.3 g (11 mmol) of 5-bromopentyl acetate, 3.82 g (27.7 mmol) of anhydrous granular potassium carbonate and 25 ml of dimethyl sulfoxide was stirred at room temperature for 20 hr. The resulting brown slurry was diluted with ether and washed with water and saturated brine. Completion of the usual work-up gave 2.59 g (100%) of 3-[[5-(acetyloxy)pentyloxy]benzaldehyde as a yellow oil which was used without further purification.

**EXAMPLE 64****Preparation of (E)-3-[3-[[5-(Acetyloxy)pentyloxy]phenyl]-2-propenoic acid methyl ester**

Using the procedure of example 28, the title compound was prepared in 80% yield from 2.6 g (10.4 mmol) of 3-[[5-(acetyloxy)pentyloxy]benzaldehyde and 4.0 g (12 mmol) of methyl (triphenylphosphoranylidene)acetate as a colorless solid, mp 65-67 °.

**EXAMPLE 65****Preparation of 3-[[5-(Acetyloxy)pentyloxy]benzenepropanoic acid methyl ester**

Using the procedure of example 29, except that methanol was used as the solvent, (E)-3-[3-[[5-(acetyloxy)pentyloxy]phenyl]-2-propenoic acid methyl ester was hydrogenated giving 3-[[5-(acetyloxy)pentyloxy]benzenepropanoic acid methyl ester as a pale-yellow oil in 97% yield.

**EXAMPLE 66****Preparation of 3-[(5-Hydroxypentyl)oxy]benzenepropanoic acid methyl ester**

5 Using the procedure of example 31, 3-[[5-(acetyloxy)pentyl]oxy]benzenepropanoic acid methyl ester was converted into 3-[(5-hydroxypentyl)oxy]benzenepropanoic acid methyl ester, a colorless oil, in 61% yield.

**EXAMPLE 67**

10

**Preparation of 3-[[5-[(Methylsulfonyl)oxy]pentyl]oxy]benzenepropanoic acid methyl ester**

Using the procedure of example 32, the 3-[(5-hydroxypentyl)oxy]benzenepropanoic acid methyl ester from the preceding example was converted into 3-[[5-[(methylsulfonyl)oxy]pentyl]oxy]benzenepropanoic acid methyl ester, an oil, in quantitative yield.

**EXAMPLE 68**

20 **Preparation of 3-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid**

Using the procedure of example 11 and starting with 0.28 g (1.4 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.48 g (1.4 mmol) of 3-[[5-[(methylsulfonyl)oxy]pentyl]oxy]-benzenepropanoic acid methyl ester, 3-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid methyl ester was obtained in 57% yield (0.36 g) as a yellow oil. This diester (0.79 mmol) was saponified with 2 ml of 3N aqueous lithium hydroxide solution in 20 ml of tetrahydrofuran at room temperature for 22 hr. Work-up as in example 4 gave crystalline 3-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid. Recrystallization from ethyl acetate-hexane gave 0.30 g (86%) of a colorless solid, mp 124-125 °.

30 Anal. Calcd. for  $C_{26}H_{32}O_6$ : C, 70.89; H, 7.32. Found: C, 70.94; H, 7.32 %.

**EXAMPLE 69****Preparation of 7-(Phenylmethoxy)-8-(phenylmethyl)-4H-1-benzopyran-4-one**

35

Using the procedure of example 1, 14.02 g (42.3 mmol) of 1-[2-hydroxy-4-(phenylmethoxy)-3-(phenylmethyl)phenyl]ethanone was converted into 7-(phenylmethoxy)-8-(phenylmethyl)-4H-1-benzopyran-4-one as a beige solid in 59% yield. An analytical specimen was obtained from another experiment by recrystallization from ether as a colorless solid, mp 108.5-109.5 °.

40 Anal. Calcd. for  $C_{23}H_{18}O_3$ : C, 80.67; H, 5.30. Found: C, 80.52; H, 5.46 %.

**EXAMPLE 70****Preparation of 2,3-Dihydro-7-hydroxy-8-(phenylmethyl)-4H-1-benzopyran-4-one**

45

Using the procedure of example 2, 5.7 g (16.6 mmol) of 7-(phenylmethoxy)-8-(phenylmethyl)-4H-1-benzopyran-4-one was catalytically hydrogenated giving 2,3-dihydro-7-hydroxy-8-(phenylmethyl)-4H-1-benzopyran-4-one as a solid in 45% yield. A sample was recrystallized from acetonitrile giving a colorless solid, mp 176-176.5 °.

50 Anal. Calcd. for  $C_{16}H_{14}O_3$ : C, 75.58; H, 5.55. Found: C, 75.34; H, 5.58 %.

**EXAMPLE 71****Preparation of 2-[(5-Hydroxypentyl)oxy]benzenepropanoic acid methyl ester**

55

Using the procedure of example 31, 2-[[5-(acetyloxy)pentyl]oxy]benzenepropanoic acid methyl ester (from example 29) was converted into 2-[(5-hydroxypentyl)oxy]benzenepropanoic acid methyl ester as a colorless viscous oil in 91.5% yield.



**EXAMPLE 72****Preparation of 2-[[5-[(Methylsulfonyl)oxy]pentyl]oxy]benzenepropanoic acid methyl ester**

5 Using the procedure of example 32, 2-[(5-hydroxypentyl)oxy]benzenepropanoic acid methyl ester was converted into 2-[[5-[(methylsulfonyl)oxy]pentyl]oxy]benzenepropanoic acid methyl ester in quantitative yield as a colorless oil which was used without further purification.

**EXAMPLE 73**

10

**Preparation of 2-[5-[[3,4-Dihydro-4-oxo-8-(phenylmethyl)-2H-1-benzopyran-7-yl]oxy]pentyl]oxy]benzenepropanoic acid**

Using the procedure of example 11 and starting with 1.2 g (4.72 mmol) of 2,3-dihydro-7-hydroxy-8-(phenylmethyl)-4H-1-benzopyran-4-one and 1.64 g (4.76 mmol) of 2-[[5-[(methylsulfonyl)oxy]pentyl]oxy]benzenepropanoic acid methyl ester, 2-[5-[[3,4-dihydro-4-oxo-8-(phenylmethyl)-2H-1-benzopyran-7-yl]oxy]pentyl]oxy]benzenepropanoic acid methyl ester was obtained in 91.5% yield (2.17 g) as a yellow oil. This diester (4.32 mmol) was saponified with 6.5 ml of 3N aqueous lithium hydroxide solution in 21 ml of tetrahydrofuran at room temperature for 48 hr. Work-up as in example 4 gave 2-[5-[[3,4-dihydro-4-oxo-8-(phenylmethyl)-2H-1-benzopyran-7-yl]oxy]pentyl]oxy]benzenepropanoic acid as an oil. This material was flash-chromatographed on silica gel eluting with ethyl acetate-hexane mixtures giving 1.0 g (47.6%) of pure acid as a solid. Recrystallization from ethyl acetate-ether gave a colorless solid, mp 117-118 °.

Anal. Calcd. for  $C_{30}H_{32}O_6$ : C, 73.75; H, 6.60. Found: C, 74.00; H, 6.61 %.

**EXAMPLE 74****Preparation of (E)-3-[2-[[5-(Acetyloxy)pentyl]oxy]phenyl]-2-propenoic acid methyl ester**

Using the procedure of example 63, 1.78 g (10 mmol) of methyl 2-hydroxy-cinnamate was alkylated with 2.3 g (11 mmol) of 5-bromopentyl acetate giving (E)-3-[2-[[5-(acetyloxy)pentyl]oxy]phenyl]-2-propenoic acid methyl ester as a pale-yellow oil in quantitative yield. The crude product was used without further purification.

**EXAMPLE 75**

35

**Preparation of (E)-3-[2-[(5-Hydroxypentyl)oxy]phenyl]-2-propenoic acid methyl ester**

Using the procedure of example 31, 3.22 g (ca. 10 mmol) of crude (E)-3-[2-[[5-(acetyloxy)pentyl]oxy]phenyl]-2-propenoic acid methyl ester was converted into 2.27 g (86%) of (E)-3-[2-[(5-hydroxypentyl)oxy]phenyl]-2-propenoic acid methyl ester as a colorless oil.

**EXAMPLE 76****Preparation of (E)-3-[2-[[5-[(Methylsulfonyl)oxy]pentyl]oxy]phenyl]-2-propenoic acid methyl ester**

45

Using the procedure of example 32, 1.09 g (4.13 mmol) of (E)-3-[2-[(5-hydroxypentyl)oxy]phenyl]-2-propenoic acid methyl ester was converted into 1.37 g (97%) of (E)-3-[2-[[5-[(methylsulfonyl)oxy]pentyl]oxy]phenyl]-2-propenoic acid methyl ester as a yellow oil.

**EXAMPLE 77****Preparation of (E)-3-[2-[5-[(5-Oxo-2-(2-propenyl)-5,6,7,8-tetrahydro-1-naphthalenyl)oxy]pentyl]oxy]phenyl]-2-propenoic acid methyl ester**

55 A mixture of 1.37 g (4 mmol) of (E)-3-[2-[[5[(methylsulfonyl)oxy]pentyl]oxy]phenyl]-2-propenoic acid methyl ester, 0.81 g (4 mmol) of 5-oxo-2-(2-propenyl)-5,6,7,8-tetrahydro-1-naphthalenol, 0.8 g (5.8 mmol) of anhydrous granular potassium carbonate, 0.08 ml of TDA-1 and 25 ml of toluene was stirred under reflux for 5.5 hr and at room temperature for 12 hr. After being treated with 0.3 g of additional potassium carbonate,

the mixture was stirred and refluxed for a further 24 hr. The mixture was cooled and diluted with ether. The organic phase was washed with water and saturated brine and work-up was completed in the usual manner giving a brown oil. This material was chromatographed on 50 g of silica gel. Elution with 1:1 hexane-ether afforded 1.72 g (96%) of (E)-3-[2-[5-[(5-oxo-2-(2-propenyl)-5,6,7,8-tetrahydro-1-naphthalenyl)-oxy]pentyloxy]phenyl]-2-propenoic acid methyl ester as a yellow-orange oil.

#### EXAMPLE 78

**Preparation of 2-[5-[(5-Oxo-2-propyl-5,6,7,8-tetrahydro-1-naphthalenyl)oxy]pentyloxy]benzenepropanoic acid methyl ester**

A mixture of 1.72 g (3.84 mmol) of (E)-3-[2-[5-[(5-oxo-2-(2-propenyl)-5,6,7,8-tetrahydro-1-naphthalenyl)-oxy]pentyloxy]phenyl]-2-propenoic acid methyl ester from the preceding example, 0.1 g of 10% palladium of carbon and 50 ml of ethyl acetate was stirred in an atmosphere of hydrogen until gas uptake ceased. The catalyst was filtered with suction on a pad of Celite and the filter cake was washed thoroughly with ethyl acetate. Concentration of the combined filtrate and washes under reduced pressure gave a yellow oil which was chromatographed on 50 g of silica gel. Elution with 4:1 hexane-ether afforded 1.35 g (78%) of 2-[5-[(5-oxo-2-propyl-5,6,7,8-tetrahydro-1-naphthalenyl)oxy]pentyloxy]benzenepropanoic acid methyl ester as a pale-yellow oil.

#### EXAMPLE 79

**Preparation of 2-[5-[(5-Oxo-2-propyl-5,6,7,8-tetrahydro-1-naphthalenyl)oxy]pentyloxy]benzenepropanoic acid**

The 2-[5-[(5-oxo-2-propyl-5,6,7,8-tetrahydro-1-naphthalenyl)oxy]pentyloxy]benzenepropanoic acid methyl ester from the preceding example (1.35 g; 2.99 mmol) and 8 ml of 1N aqueous sodium hydroxide solution in 15 ml of methanol was stirred and refluxed for 1.5 hr. After being cooled, the resulting solution was diluted with water and acidified with 3N hydrochloric acid. Work-up with ether in the usual manner gave 1.3 g (100%) of 2-[5-[(5-oxo-2-propyl-5,6,7,8-tetrahydro-1-naphthalenyl)oxy]pentyloxy]benzenepropanoic acid as an orange oil.

#### EXAMPLE 80

**Preparation of 2-[(7-Bromoheptyl)oxy]-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester**

Starting with 0.381 g (1.03 mmol) of 5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester and 2.13 g (8.26 mmol) of 1,7-dibromoheptane, the title compound was obtained as a colorless oil in 81.6% yield using the procedure of example 21.

Anal. Calcd. for  $C_{28}H_{35}BrO_6$ : C, 61.43; H, 6.44; Br, 14.60. Found: C, 61.82; H, 6.45; Br, 14.89 %.

#### EXAMPLE 81

**Preparation of 5-[(3-Carboxyphenyl)carbonyl]-2-[7-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]heptyloxy]benzenepropanoic acid**

Starting with 0.153 g (0.74 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.41 g (0.74 mmol) of 2-[(7-bromoheptyl)oxy]-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester, the title compound (0.286 g; 77.8% overall yield) was obtained as a white solid, mp 152-153 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 22.

Anal. Calcd. for  $C_{36}H_{40}O_9$ : C, 70.11; H, 6.54. Found: C, 70.28; H, 6.84 %.

**EXAMPLE 82****Preparation of 2-[(8-Bromooctyl)oxy]-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester**

Starting with 0.370 g (1.0 mmol) of 5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester and 2.17 g (7.98 mmol) of 1,8-dibromooctane, the title compound was obtained as a colorless oil in 72.6% yield using the procedure of example 21.

Anal. Calcd. for  $C_{29}H_{37}BrO_6$ : C, 62.03; H, 6.64; Br, 14.23. Found: C, 62.06; H, 6.59; Br, 14.38 %.

**EXAMPLE 83****Preparation of 5-[(3-Carboxyphenyl)carbonyl]-2-[8-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]octyloxy]benzenepropanoic acid**

Starting with 0.128 g (0.62 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.349 g (0.62 mmol) of 2-[(8-bromooctyl)oxy]-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester, the title compound (0.232 g; 76.3% overall yield) was obtained as a white solid, mp 112-117 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 22.

Anal. Calcd. for  $C_{37}H_{42}O_9$ : C, 70.46; H, 6.71. Found: C, 69.94; H, 6.98 %.

**EXAMPLE 84****Preparation of 2-[(5-Bromopentyl)oxy]-5-[[4-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester**

Starting with 0.484 g (1.31 mmol) of 5-[[4-(ethoxycarbonyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester and 2.4 g (10.44 mmol) of 1,5-dibromopentane, the title compound was obtained in 72.6% yield as a white solid, mp 76.5 -78 °, using the procedure of example 21.

Anal. Calcd. for  $C_{26}H_{31}BrO_6$ : C, 60.12; H, 6.02; Br, 15.38. Found: C, 60.28; H, 6.00; Br, 15.56 %.

**EXAMPLE 85****Preparation of 5-[(4-Carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid**

Starting with 0.157 g (0.76 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.391 g (0.75 mmol) of 2-[(5-bromopentyl)oxy]-5-[[4-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester, the title compound (0.240 g; 63.6% overall yield) was obtained as a white solid, mp 175-177 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 22.

Anal. Calcd. for  $C_{34}H_{36}O_9$ : C, 69.37; H, 6.17. Found: C, 69.36; H, 6.26 %.

**EXAMPLE 86****Preparation of 4-[(5-Bromopentyl)oxy]-3-(3-ethoxy-3-oxopropyl)- $\delta$ -oxobenzenepentanoic acid ethyl ester**

Starting with 0.332 g (0.99 mmol) of 3-(3-ethoxy-3-oxopropyl)-4-hydroxy- $\delta$ -oxobenzenepentanoic acid ethyl ester and 1.16 g (5.04 mmol) of 1,5-dibromopentane, the title compound was obtained in 85.7% yield as a white solid, mp 48-49 °, using the procedure of example 21.

Anal. Calcd. for  $C_{29}H_{33}BrO_6$ : C, 56.91; H, 6.85; Br, 16.64. Found: C, 56.59; H, 6.83; Br, 16.76 %.

**EXAMPLE 87****Preparation of 3-(2-Carboxyethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]- $\delta$ -oxobenzenepentanoic acid**

5 Stating with 0.135 g (0.66 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.31 g (0.64 mmol) of 4-[(5-bromopentyl)oxy]-3-(3-ethoxy-3-oxopropyl)- $\delta$ -oxobenzenepentanoic acid ethyl ester, the title compound (0.190 g; 62.8% overall yield) was obtained as a white solid, mp 151-153.5 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 22.

10 Anal. Calcd. for  $C_{31}H_{38}O_9$ : C, 67.13; H, 6.91. Found: C, 66.81; H, 6.99 %.

**EXAMPLE 88****Preparation of 4-[(5-Bromopentyl)oxy]-3-(3-ethoxy-3-oxopropyl)- $\gamma$ -oxobenzenebutanoic acid ethyl ester**

15 Starting with 0.458 g (1.42 mmol) of 3-(3-ethoxy-3-oxopropyl)-4-hydroxy- $\gamma$ -oxobenzenebutanoic acid ethyl ester and 1.65 g (7.29 mmol) of 1,5-dibromopentane, the title compound was obtained in 80.6% yield as a white solid, mp 40-41 °, using the procedure of example 21.

20 Anal. Calcd. for  $C_{22}H_{31}BrO_6$ : C, 56.06; H, 6.63; Br, 16.95. Found: C, 55.78; H, 6.60; Br, 17.05 %.

**EXAMPLE 89****Preparation of 3-(2-Carboxyethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]- $\gamma$ -oxobenzenebutanoic acid**

25 Starting with 0.156 g (0.76 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.357 g (0.76 mmol) of 4-[(5-bromopentyl)oxy]-3-(3-ethoxy-3-oxopropyl)- $\gamma$ -oxobenzenebutanoic acid ethyl ester, the title compound (0.237 g; 63.8% overall yield) was obtained as a white solid, mp 181.5-184 ° (recrystallized from ethanol-ethyl acetate), using the procedure of example 22.

30 Anal. Calcd. for  $C_{30}H_{36}O_9$ : C, 66.65; H, 6.71. Found: C, 66.69; H, 6.76 %.

**EXAMPLE 90****Preparation of 2-Methoxy-5-(1-oxo-1H-2-benzopyran-3-yl)benzenepropanoic acid ethyl ester, 2-Hydroxy-5-(1-oxo-1H-2-benzopyran-3-yl)benzenepropanoic acid ethyl ester and 5-[[2-(2-Ethoxy-2-oxoethyl)phenyl]carbonyl]-2-methoxybenzenepropanoic acid ethyl ester**

35 A mixture of 6.41 g (39.53 mmol) homophthalic anhydride, 8.21g (39.42 mmol) of 2-methoxybenzenepropanoic acid ethyl ester, 21.03 g (0.158 mol) of aluminum chloride and 75 ml of dry methylene chloride was stirred and heated in an oil bath kept at ca. 45 ° for 21 hr. The mixture was cooled to room temperature and then poured onto crushed ice. Aqueous sulfuric acid (3N, 150 ml) was added and the mixture was extracted three times with ether. The combined ethereal solution was washed twice with water and three times with saturated sodium bicarbonate solution (the organic phase was discarded). After being  
40 cooled in an ice bath, the aqueous alkaline phase was acidified with concentrated hydrochloric acid and the resulting solution was extracted once with ether and twice with ethyl acetate. The organic extracts were combined and processed in the usual manner to give 12.61 g of a white solid residue. This material was dissolved in 500 ml of ethanol and concentrated sulfuric acid (8 ml) was added. The resulting mixture was heated at reflux for 5.7 hr and then cooled to room temperature. Most of the solvent was removed under  
45 aspirator pressure. The residue was taken up in ethyl acetate and processed in the usual manner (the organic solution was additionally washed with saturated sodium bicarbonate solution). The crude product was purified by flash chromatography on 500 g of silica gel eluting with hexane-ethyl acetate (4:1 then 2:1) to give a less polar fraction (6.55 g) and a more polar fraction (2.34 g). Crystallization of the less polar fraction from ethanol afforded 2.42 g of 2-methoxy-5-(1-oxo-1H-2-benzopyran-3-yl)benzenepropanoic acid  
50 ethyl ester as colorless needles, mp 105-105.5 °.

Anal. Calcd. for  $C_{21}H_{20}O_5$ : C, 71.58; H, 5.72. Found: C, 71.59; H, 5.71 %.

From the remaining mother liquor (4.13 g), 1.3 g was purified further by flash chromatography on 100 g of silica gel eluting with 4:1 hexane-ethyl acetate and gave 1.26 g of 5-[[2-(2-ethoxy-2-oxoethyl)phenyl]-

carbonyl]-2-methoxybenzenepropanoic acid ethyl ester as a colorless oil.

Anal. Calcd. for  $C_{23}H_{26}O_6$ : C, 69.33; H, 6.58. Found: C, 69.29; H, 6.55 %.

Similarly, crystallization of the more polar fraction from ethanol afforded 0.56 g of 2-hydroxy-5-(1-oxo-1H-2-benzopyran-3-yl)benzenepropanoic acid ethyl ester as an off-white solid, mp 179-180 °.

5 Anal. Calcd. for  $C_{20}H_{18}O_5$ : C, 71.00; H, 5.36. Found: C, 70.78; H, 5.33 %.

#### EXAMPLE 91

##### 10 Preparation of 2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-5-(1-oxo-1H-2-benzopyran-3-yl)benzenepropanoic acid ethyl ester

A mixture of 0.352 g (0.99 mmol) of 7-[(5-bromopentyl)oxy]-2,3-dihydro-8-propyl-4H-1-benzopyran-4-one, 0.346 g (1.02 mmol) of 2-hydroxy-5-(1-oxo-1H-2-benzopyran-3-yl)benzenepropanoic acid ethyl ester, 0.574 g (4.15 mmol) of anhydrous granular potassium carbonate and 20.9 ml of 2-butanone was stirred and  
15 refluxed for 45 hr. The resulting slurry was filtered with suction and the solids were washed thoroughly with ethyl acetate. The filtrate and washes were combined and concentrated in vacuo and the residue was purified by flash chromatography on 75 g of silica gel eluting with 3:1 hexane-ethyl acetate and afforded 0.352 g (58.1%) of the title compound as a white solid, mp 143.5-144 °.

Anal. Calcd for  $C_{37}H_{40}O_8$ : C, 72.53; H, 6.58. Found: C, 72.68; H, 6.47 %.

20

#### EXAMPLE 92

##### 25 Preparation of 5-[2-(2-Carboxyphenyl)-1-oxoethyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid

A mixture of 0.145 g (0.24 mmol) of 2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-5-(1-oxo-1H-2-benzopyran-3-yl)benzenepropanoic acid ethyl ester in 5 ml of tetrahydrofuran and 5 ml of water was treated with 29.8 mg (0.71 mmol) of lithium hydroxide monohydrate and the mixture was  
30 stirred for 47 hr. After being acidified with 16 ml of 3N aqueous sulfuric acid the resulting mixture was worked up in the usual manner. The crude product was crystallized from hexane-ethyl acetate to give 0.114 g (79.6%) of the title compound as a white solid, mp 178-182 °.

Anal. Calcd. for  $C_{35}H_{38}O_9$ : C, 69.75; H, 6.36. Found: C, 69.66; H, 6.25 %.

#### Example 93

35

##### Preparation of 5-[[2-(2-Ethoxy-2-oxoethyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester

A mixture of 1.07 g (2.69 mmol) of 5-[[2-(2-ethoxy-2-oxoethyl)phenyl]carbonyl]-2-methoxybenzenepropanoic acid ethyl ester and 3.63 g (31.41 mmol) of pyridine hydrochloride was heated at 220-260 °  
40 for 40 min and then cooled to room temperature. Aqueous 3N sulfuric acid (40 ml) was added, and the mixture was worked-up with ethyl acetate in the usual manner. The crude product was dissolved in 150 ml of ethanol. To this solution were added 3 ml of thionyl chloride and the resulting solution was heated at reflux for 16 hr. The solvent was removed in vacuo and the crude product was purified by flash  
45 chromatography on 120 g of silica gel eluting with 3:1 hexane-ethyl acetate. This afforded 0.469 g (45.4%) of the title compound as a pale yellow oil.

#### EXAMPLE 94

##### 50 Preparation of 2-[(5-Bromopentyl)oxy]-5-[[2-(2-ethoxy-2-oxoethyl)phenyl]carbonyl]-benzenepropanoic acid ethyl ester

Starting with 0.436 g (1.13 mmol) of 5-[[2-(2-ethoxy-2-oxoethyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester and 6.80 g (29.57 mmol) of 1,5-dibromopentane, the title compound was  
55 obtained as a pale yellow oil in 74% yield using the procedure of example 21.

Anal. Calcd. for  $C_{27}H_{33}BrO_6$ : C, 60.79; H, 6.24; Br, 14.98. Found: C, 60.38; H, 6.21; Br, 15.14 %.

**EXAMPLE 95****Preparation of 5-[[2-(Carboxymethyl)phenyl]carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid**

Starting with 0.153 g (0.74 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.394 g (0.74 mmol) of 2-[(5-bromopentyl)oxy]-5-[[2-(2-ethoxy-2-oxoethyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester, the title compound (0.103 g, 26.7% overall yield) was obtained as a white solid, mp 105-108.5 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 22.

Anal. Calcd. for  $C_{35}H_{38}O_9$ : C, 69.75; H, 6.36. Found: C, 69.60; H, 6.45 %.

**EXAMPLE 96****Preparation of 5-[[3-(Ethoxycarbonyl)phenyl]carbonyl]-2-[(trifluoromethyl)sulfonyl]oxy]benzenepropanoic acid ethyl ester**

To a solution of 8.50 g (22.95 mmol) of 5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester in 20 ml of pyridine cooled in an ice bath were added slowly 4.2 ml (24.97 mmol) of trifluoromethanesulfonic anhydride. After being stirred for 43 hr, the reaction mixture was treated with 100 ml of water and worked-up with ether in the usual manner. The crude product obtained was purified by flash chromatography on 600 g of silica gel eluting with 4:1 hexane-ethyl acetate. This afforded 10.09g (87.5%) of the title compound as a colorless oil.

Anal. Calcd. for  $C_{22}H_{21}F_3O_8S$ : C, 52.59; H, 4.21; F, 11.34; S, 6.38. Found: C, 52.55; H, 4.20; F, 11.10; S, 6.68 %.

**EXAMPLE 97****Preparation of (Z)-5-[[3-(Ethoxycarbonyl)phenyl]carbonyl]-2-(6-hydroxy-1-hexenyl)benzenepropanoic acid ethyl ester and (E)-5-[[3-(Ethoxycarbonyl)phenyl]carbonyl]-2-(6-hydroxy-1-hexenyl)benzenepropanoic acid ethyl ester**

A mixture of 1.78 g (3.55 mmol) of 5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-[(trifluoromethyl)sulfonyl]oxy]benzenepropanoic acid ethyl ester, 1.476 g (3.73 mmol) of (E/Z)-tri-n-butyl-(6-hydroxy-1-hexenyl)-stannane, 0.456 g (10.76 mmol) of lithium chloride, 0.24 g (0.21 mmol) of tetrakis(triphenylphosphine)-palladium, a few crystals of 2,6-di-tert-butyl-4-methylphenol and 20 ml of dioxane was stirred and heated at reflux for a total of 2.75 hr. After being cooled to room temperature, the reaction mixture was treated with 2 ml of pyridine and 4 ml of a solution of hydrogenfluoride in pyridine/tetrahydrofuran (ca. 1.2N) and stirring was continued overnight. The mixture was taken up in 200 ml of ether, filtered through Celite and worked up in the usual manner. The crude product was purified by flash chromatography on 200 g of silica gel eluting with 2:1 hexane-ethyl acetate. This afforded 0.17 g (10.6%) of (Z)-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-(6-hydroxy-1-hexenyl)benzenepropanoic acid ethyl ester as a colorless oil. Further elution gave 0.516 g (32.2%) of mixed fractions followed by 0.789 g (49.2%) of (E)-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-(6-hydroxy-1-hexenyl)benzenepropanoic acid ethyl ester as a white solid, mp 48-50 °.

Anal. Calcd for  $C_{27}H_{32}O_6$ : C, 71.66; H, 7.13. Found: C, 71.48; H, 7.11 %.

**EXAMPLE 98****Preparation of 2-(6-Bromohexyl)-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester**

To a solution of 0.686 g (1.52 mmol) of a mixture of (E/Z)-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-(6-hydroxy-1-hexenyl)benzenepropanoic acid ethyl ester in 5 ml of ethanol and 5 ml of ethyl acetate was added 110 mg of 10% Pd/C catalyst, and the mixture was hydrogenated at atmospheric pressure until no further hydrogen uptake could be observed. The mixture was filtered through Celite, the filter cake was washed thoroughly with ethyl acetate and the filtrate and washes were combined and concentrated in vacuo to give 0.563 g of the saturated product. To this was added 0.822 g (2.48 mmol) of carbon tetrabromide, 0.65 g (2.48 mmol) of triphenylphosphine and 10 ml of ether, and the mixture was stirred overnight. The mixture was filtered through Celite, the filter cake was washed thoroughly with ether and the combined

filtrate and washes concentrated in vacuo. The crude product was purified by flash chromatography on 50 g of silica gel eluting with 6:1 hexane-ethyl acetate and afforded 0.486 g (61.9% overall yield) of the title compound as a colorless oil.

Anal. Calcd. for  $C_{27}H_{33}BrO_5$ : C, 62.67; H, 6.43; Br, 15.42. Found: C, 62.43; H, 6.43; Br, 15.18 %.

#### EXAMPLE 99

##### Preparation of 5-[(3-Carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid

Starting with 0.169 g (0.82 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.425 g (0.82 mmol) of 2-(6-bromohexyl)-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester, the title compound (0.157 g; 34.7% overall yield) was obtained as a white solid, mp 137-139 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 22.

Anal. Calcd. for  $C_{35}H_{38}O_8$ : C, 71.66; H, 6.53. Found: C, 71.25; H, 6.89 %.

#### EXAMPLE 100

##### Preparation of (E)-2-(6-Bromo-1-hexenyl)-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester

Starting with 0.660 g (1.46 mmol) of (E)-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]-2-(6-hydroxy-1-hexenyl)-benzenepropanoic acid ethyl ester, the title compound (0.667 g; 88.8%) was obtained as a colorless oil using the procedure of example 98 but omitting the hydrogenation step.

#### EXAMPLE 101

##### Preparation of (E)-5-[(3-Carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]-1-hexenyl]benzenepropanoic acid

Starting with 0.242 g (1.17 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.604 g (1.17 mmol) of (E)-2-(6-bromo-1-hexenyl)-5-[[3-(ethoxycarbonyl)phenyl]carbonyl]benzenepropanoic acid ethyl ester, the title compound was obtained (97 mg; 15.8% overall yield) as a white solid, mp 105-109 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 22.

Anal. Calcd. for  $C_{35}H_{36}O_8$ : C, 71.90; H, 6.21. Found: C, 71.61; H, 6.16 %.

#### EXAMPLE 102

##### Preparation of 2-[(5-Hexynyl)oxy]benzenepropanoic acid methyl ester

A mixture of 0.98 g (10 mmol) of 5-hexyn-1-ol, 1.98 g (11 mmol) of 2-hydroxybenzenepropanoic acid methyl ester, 2.88 g (11 mmol) of triphenylphosphine, 1.91 g (11 mmol) of diethyl azodicarboxylate and 220 ml of dry tetrahydrofuran was stirred at room temperature for 100 hr and then concentrated under reduced pressure. The residue was triturated with 9:1 hexane-ether. The solid was filtered with suction and washed with the same solvent mixture. The filtrate and washes were combined and concentrated in vacuo. Flash chromatography of the residue on silica gel eluting with 9:1 hexane-ether gave 2 g (77%) of 2-[(5-hexynyl)oxy]benzenepropanoic acid methyl ester as a colorless oil.

#### EXAMPLE 103

##### Preparation of 2,3-Dihydro-8-propyl-7-[(trifluoromethyl)sulfonyl]oxy]-4H-1-benzopyran-4-one

A solution of 0.824 g (4 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 4 ml of dry pyridine in 20 ml of dichloromethane was stirred with cooling to 0 °, while 1.69 g (6 mmol) of trifluoromethanesulfonic anhydride was added dropwise. The solution was stirred at 0 ° for 1 hr and at room temperature for 2 hr. After being recooled, the reaction mixture was treated with an additional 0.5 ml (3 mmol) of trifluoromethanesulfonic anhydride and stirring was continued at 0 ° for 1 hr and at room temperature for 2 hr. The reaction mixture was stored at 0-5 ° overnight before being poured into cold 3N

hydrochloric acid. Work-up with ether in the usual manner (the organic extract was additionally washed with saturated sodium bicarbonate solution) gave an oily product which was flash- chromatographed on silica gel. Elution with 1:1 hexaneether gave 1.14 g (84%) of 2,3-dihydro-8-propyl-7-[[trifluoromethyl)sulfonyl]-oxy]-4H-1-benzopyran-4-one as a yellow oil.

#### EXAMPLE 104

**Preparation of 2-[6-(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-5-hexynyloxy]-benzenepropanoic acid methyl ester**

A mixture of 1.14 g (3.37 mmol) of 2,3-dihydro-8-propyl-7-[[trifluoromethyl)sulfonyl]oxy]-4H-1-benzopyran-4-one, 0.94 g (3.62 mmol) of 2-[(5-hexynyl)oxy]benzenepropanoic acid methyl ester, 4.9 ml of dry triethylamine, 0.197 g (0.28 mmol) of dichlorobis(triphenylphosphine)palladium (II) and 21 ml of dry dimethylformamide was stirred and heated at 100 ° for 3 hr. The mixture was cooled, poured into ice-water and worked-up with ether in the usual manner. The orange-red oily residue was flash-chromatographed on silica gel. Elution with 1:1 hexane-ether gave 1.25 g (83 %) of 2-[6-(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-5-hexynyloxy]benzenepropanoic acid methyl ester as a yellow oil.

#### EXAMPLE 105

**Preparation of 2-[6-(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)hexyloxy]benzenepropanoic acid methyl ester**

Catalytic hydrogenation of 2-[6-(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-5-hexynyloxy]-benzenepropanoic acid methyl ester in methanol was carried out using the procedure of example 51. 2-[6-(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)hexyloxy]benzenepropanoic acid methyl ester was obtained as a colorless oil in 86% yield.

#### EXAMPLE 106

**Preparation of 2-[6-(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)hexyloxy]benzenepropanoic acid**

A mixture of 0.65 g (1.44 mmol) of 2-[6-(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)hexyloxy]-benzenepropanoic acid methyl ester, 2 ml of 3N aqueous lithium hydroxide solution and 30 ml of tetrahydrofuran was stirred at room temperature for 24 hr and then concentrated in vacuo. The residue was diluted with water and extracted 3 times with ether (the ether extracts were discarded). The aqueous alkaline solution was acidified with 3N hydrochloric acid and worked-up with ether in the usual manner. The oily residue was chromatographed on silica gel. Elution with 2:1 toluene-ethyl acetate containing acetic acid afforded 0.5 g (79.3%) of 2-[6-(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)hexyloxy]-benzenepropanoic acid as viscous colorless oil.

Anal. Calcd. for  $C_{27}H_{34}O_5$ : C, 73.94; H, 7.81. Found: C, 73.83; H, 7.69 %.

#### EXAMPLE 107

**Preparation of 2-[6-(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-5-hexynyloxy]-benzenepropanoic acid**

A 0.5 g (1.12 mmol) sample of 2-[6-(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-5-hexynyloxy]-benzenepropanoic acid methyl ester from example 104 was saponified using the procedure of example 106. The crude acid product was purified by flash chromatography on silica gel eluting with toluene-ethyl acetate mixtures containing 2% acetic acid and recrystallization from acetonitrile giving 2-[6-(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)-5-hexynyloxy]benzenepropanoic acid as a colorless solid, mp 88-92 °.



**EXAMPLE 108****Preparation of (E)-3-[2-[(5-Bromopentyl)oxy]phenyl]-2-propenoic acid methyl ester**

5 A mixture of 0.64 g (3.59 mmol) of methyl 2-hydroxycinnamate, 6.6. g (28.7 mmol) of 1,5-dibromopentane, 2 g (14.5 mmol) of anhydrous granular potassium carbonate and 25 ml of acetonitrile was stirred and refluxed for 24 hr. The resulting slurry was cooled, diluted with ether and filtered with suction. The solids were washed well with ether. The filtrate and washes were combined and concentrated under reduced pressure. The oily residue was flash-chromatographed on silica gel eluting with 5:1 hexane-ether giving 1 g  
10 (85%) of (E)-3-[2-[(5-bromopentyl)oxy]phenyl]-2-propenoic acid methyl ester as a solid.

**EXAMPLE 109****Preparation of (E)-3-[2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]phenyl]-2-propenoic acid**

Using the procedure of example 4 and starting with 0.5 g (1.5 mmol) of (E)-3-[2-[(5-bromopentyl)oxy]phenyl]-2-propenoic acid methyl ester and 0.3 g (1.45 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one, (E)-3-[2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]phenyl]-2-propenoic acid was obtained in 24% overall yield after purification by flash chromatography (silica gel, chloroform:methanol-acetic acid) and recrystallization from acetonitrile as a colorless solid, mp 123-126 °.  
20

Anal. Calcd. for  $C_{26}H_{30}O_6$ : C, 71.23; H, 6.84. Found: C, 71.01; H, 6.97 %.

**EXAMPLE 110****Preparation of rac-4-[3-Formyl-4-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]phenoxy]butanoic acid ethyl ester**

A 1.2 g (2.88 mmol) sample of rac-4-[3-formyl-4-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexyn-1-yl]phenoxy]butanoic acid ethyl ester from example 49 was hydrogenated in ethyl acetate using 80 mg of 10% palladium on carbon at room temperature under 1 atmosphere of hydrogen. When the reduction was complete, the catalyst was filtered off with suction and the filtrate concentrated under reduced pressure giving rac-4-[3-formyl-4-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]phenoxy]butanoic acid ethyl ester as a pale-yellow oil in quantitative yield.  
30

**EXAMPLE 111****Preparation of rac-(E)-4-[3-(3-Methoxy-3-oxo-1-propenyl)-4-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]phenoxy]butanoic acid ethyl ester**

Using the procedure of example 28 and starting with 1.2 g (2.88 mmol) of rac-4-[3-formyl-4-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]phenoxy]butanoic acid ethyl ester from the preceding example and 1.12 g (3.36 mmol) of methyl (triphenylphosphoranylidene) acetate, rac-(E)-4-[3-(3-methoxy-3-oxo-1-propenyl)-4-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]phenoxy]butanoic acid ethyl ester was prepared in 66% yield (0.9 g) as a colorless oil.  
40  
45

**EXAMPLE 112****Preparation of (E)-4-[4-(6-Hydroxyhexyl)-3-(3-methoxy-3-oxo-1-propenyl)phenoxy]butanoic acid methyl ester**

Using the procedure of example 52, rac-(E)-4-[3-(3-methoxy-3-oxo-1-propenyl)-4-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]phenoxy]butanoic acid ethyl ester (0.9 g; 1.89 mmol) was converted into (E)-4-[4-(6-hydroxyhexyl)-3-(3-methoxy-3-oxo-1-propenyl)phenoxy]butanoic acid methyl ester as a pale-yellow oil in 92% yield (0.66 g).  
55

**EXAMPLE 113****Preparation of (E)-4-[3-(3-Methoxy-3-oxo-1-propenyl)-4-[6-[(methylsulfonyl)oxy]hexyl]phenoxy]-butanoic acid methyl ester**

Using the procedure of example 32, (E)-4-[4-(6-hydroxyhexyl)-3-(3-methoxy-3-oxo-1-propenyl)phenoxy]-butanoic acid methyl ester (0.66 g; 1.74 mmol) was converted into (E)-4-[3-(3-methoxy-3-oxo-1-propenyl)-4-[6-[(methylsulfonyl)oxy]hexyl]phenoxy]butanoic acid methyl ester as a pale-yellow oil in 96% yield (0.76 g).

**EXAMPLE 114****Preparation of (E)-4-[3-(2-Carboxyethenyl)-4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]phenoxy]butanoic acid**

Using the procedure of example 11 and starting with 0.26 g (1.3 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.76 g (1.3 mmol) of (E)-4-[3-(3-methoxy-3-oxo-1-propenyl)-4-[6-[(methylsulfonyl)oxy]hexyl]phenoxy]butanoic acid methyl ester, (E)-4-[3-(2-carboxyethenyl)-4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]phenoxy]butanoic acid methyl ester was obtained in 95% yield (0.36 g) as a colorless oil which crystallized on standing. Recrystallization from ethyl acetate-hexane gave 0.51 g (69%) of a colorless solid, mp 65-66 °. A 0.2 g (0.35 mmol) sample of diester prepared in this way was saponified with 2 ml of 3N aqueous lithium hydroxide solution in 10 ml of tetrahydrofuran at room temperature for 22 hr. Work-up as in example 4 gave a crude acid product which was purified by chromatography on silica gel (toluene-ethyl acetate containing 2% acetic acid) and recrystallization from acetonitrile. There was obtained 0.1 g (53%) of (E)-4-[3-(2-carboxyethenyl)-4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-phenoxy]butanoic acid as an off-white solid mp 140-143 °.

Anal. Calcd. for  $C_{31}H_{38}O_8$ : C, 69.14; H, 7.06. Found: C, 68.83; H, 7.11 %.

**EXAMPLE 115****Preparation of 1-[2-Hydroxy-4-(phenylmethoxy)-3-pentylphenyl]ethanone**

A mixture of 3.11 g (14 mmol) of 2,4-dihydroxy-3-pentylacetophenone, 1.67 ml (14 mmol) of benzyl bromide, 7.73 g (56 mmol) of anhydrous granular potassium carbonate and 31 ml of N,N-dimethylformamide was stirred at room temperature for 3 days and then concentrated in vacuo. The residue was flash chromatographed on silica gel eluting with hexane-ether mixtures. There was obtained 1.42 g (32.5%) of 1-[2-hydroxy-4-(phenylmethoxy)-3-pentylphenyl]ethanone as a solid. A sample was recrystallized from ether-hexane giving a colorless solid, mp 61-62 °.

Anal. Calcd. for  $C_{20}H_{24}O_3$ : C, 76.90; H, 7.74. Found: C, 76.73; H, 7.76 %.

**EXAMPLE 116****Preparation of 7-(Phenylmethoxy)-8-pentyl-4H-1-benzopyran-4-one**

Using the procedure of example 1, 1.4 g (4.48 mmol) of 1-[2-hydroxy-4-(phenylmethoxy)-3-pentylphenyl]ethanone was converted into 7-(phenylmethoxy)-8-pentyl-4H-1-benzopyran-4-one as a beige solid in 55% yield. An analytical specimen was obtained by recrystallization from ether as a colorless solid, mp 65.5-67 °.

Anal. Calcd. for  $C_{21}H_{22}O_3$ : C, 78.26; H, 6.83. Found: C, 77.99; H, 6.92 %.

**EXAMPLE 117****Preparation of 2,3-Dihydro-7-hydroxy-8-pentyl-4H-1-benzopyran-4-one**

Using the procedure of example 2, 3.22 g (10 mmol) of 7-(phenylmethoxy)-8-pentyl-4H-1-benzopyran-4-one was catalytically hydrogenated giving 2,3-dihydro-7-hydroxy-8-pentyl-4H-1-benzopyran-4-one as a solid in 66% yield. A sample was recrystallized from acetonitrile giving a colorless solid, mp 132-133.5 °.

Anal. Calcd. for  $C_{14}H_{18}O_3$ : C, 71.77; H, 7.24. Found: C, 71.71; H, 7.67 %.

**EXAMPLE 118****Preparation of 2-[5-[(3,4-Dihydro-4-oxo-8-pentyl-2H-1-benzopyran-7-yl)-oxy]pentyloxy]-benzenepropanoic acid**

5

Using the procedure of example 11 and starting with 1.25 g (5.34 mmol) of 2,3-dihydro-7-hydroxy-8-pentyl-4H-1-benzopyran-4-one and 1.64 g (4.76 mmol) of 2-[[5-[(methylsulfonyl)oxy]pentyloxy]-benzenepropanoic acid methyl ester (from example 72), 2-[5-[(3,4-dihydro-4-oxo-8-pentyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid methyl ester was obtained in 98% yield (2.52 g) as a pale-yellow oil. This diester (5.18 mmol) was saponified with 7.8 ml of 3N aqueous lithium hydroxide solution in 25 ml of tetrahydrofuran at room temperature for 48 hr. Work-up as in example 4 gave 2-[5-[(3,4-dihydro-4-oxo-8-pentyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid as an oil. This material was flash-chromato-graphed on silica gel eluting with ethyl acetate-hexane mixtures giving 0.69 g (28.5%) of pure acid as a solid. Recrystallization from acetonitrile gave a colorless solid, mp 86-87 °.

15 Anal. Calcd. for  $C_{28}H_{36}O_6$ : C, 71.70; H, 7.68. Found: C, 71.30; H, 7.64 %.

**EXAMPLE 119****Preparation of Trifluoromethanesulfonic acid 2-oxo-2H-1-benzopyran-5-yl ester**

20

A mixture of 1.62 g (10 mmol) of 5-hydroxycoumarin and 10 ml of dry pyridine in 25 ml of dichloromethane was stirred with ice-bath cooling while 4.5 g (16 mmol) of trifluoromethanesulfonic anhydride was added dropwise. The mixture was stirred in the cold for 30 min and then allowed to warm to room temperature and stirred for an additional 30 min before being poured into 3N hydrochloric acid. Work-up with ether in the usual manner gave a yellow solid. Flash chromatography on silica gel eluting with 2:1 hexane:ethyl acetate afforded 2.6 g (88.4%) of trifluoromethanesulfonic acid 2-oxo-2H-1-benzopyran-5-yl ester as an off-white solid, mp 104-105 °.

Anal. Calcd. for  $C_{10}H_5F_3O_5S$ : C, 40.83; H, 1.71. Found: C, 40.65; H, 1.59 %.

**EXAMPLE 120****Preparation of rac-5-[6-[(Tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]-2H-1-benzopyran-2-one**

A mixture of 1.47 g (5 mmol) of trifluoromethanesulfonic acid 2-oxo-2H-1-benzopyran-5-yl ester, 1.0 g (5.5 mmol) of rac-6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexyne, 75 mg of cuprous iodide, 0.3 g (0.428 mmol) of dichlorobis(triphenylphosphine)palladium (II), 7.5 ml of triethylamine and 35 ml of dry N,N-dimethylformamide was stirred and heated at 100 ° for 24 hr. The reaction mixture was cooled, poured into water and worked-up with ether in the usual manner. The dark-brown, oily residue was flash-chromatographed on silica gel. Elution with 2:1 hexane-ethyl acetate gave 1.09 g (67%) of rac-5-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]-2H-1-benzopyran-2-one as an orange oil.

40

**EXAMPLE 121****Preparation of rac-(E)-3-[2-Hydroxy-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-2-propenoic acid methyl ester**

45

A solution of 1.09 g (3.3 mmol) of rac-5-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]-2H-1-benzopyran-2-one and 1.8 ml (7.9 mmol) of 25% methanolic sodium methoxide in 5 ml of methanol was stirred and refluxed for 24 hr and then concentrated under reduced pressure. The residue was treated with 1N hydrochloric acid and worked-up with ethyl acetate in the usual manner (the organic extracts were additionally washed with saturated aqueous sodium bicarbonate solution). The residue was purified by flash chromatography on silica gel eluting with 2:1 hexane-ether. There was obtained 0.7 g (59%) of rac-(E)-3-[2-hydroxy-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-2-propenoic acid methyl ester as a yellow oil. Trituration of a sample prepared in this way with hexane gave a colorless solid, mp 66-67.5 °.

55 Anal. Calcd. for  $C_{21}H_{26}O_5$ : C, 70.37; H, 7.31. Found: C, 70.24; H, 7.33 %.

**EXAMPLE 122****Preparation of rac-(E)-5-[2-(3-Methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]pentanoic acid ethyl ester**

5

A mixture of 0.7 g (1.95 mmol) of rac-(E)-3-[2-hydroxy-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-2-propenoic acid methyl ester, 0.45 g (2.14 mmol) of ethyl 5-bromovalerate, 0.75 g (5.4 mmol) of anhydrous granular potassium carbonate and 8 ml of dimethyl sulfoxide was stirred at room temperature for 24 hr. The resulting mixture was poured into water and worked-up with ether in the usual manner. The crude product was flash-chromatographed on silica gel eluting with 2:1 hexane-ethyl acetate and afforded 0.86 g (90%) of rac-(E)-5-[2-(3-methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]pentanoic acid ethyl ester as a colorless oil.

**EXAMPLE 123**

15

**Preparation of rac-2-(5-Ethoxy-5-oxopentylloxy)-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester**

A 0.86 g (1.76 mmol) sample of rac-(E)-5-[2-(3-methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]pentanoic acid ethyl ester was hydrogenated in 50 ml of methanol, over 50 mg of 10% palladium on carbon at room temperature and 1 atmosphere. Rac-2-(5-ethoxy-5-oxopentylloxy)-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester, an oil, was isolated by filtration of the catalyst and concentration of the filtrate in quantitative yield.

**EXAMPLE 124****Preparation of 2-(6-Hydroxyhexyl)-6-(5-methoxy-5-oxopentylloxy)benzenepropanoic acid methyl ester**

Using the procedure of example 52, rac-2-(5-ethoxy-5-oxopentylloxy)-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester (0.87 g; 1.76 mmol) was converted into 2-(6-hydroxyhexyl)-6-(5-methoxy-5-oxopentylloxy)benzenepropanoic acid methyl ester as a colorless oil in 53% yield.

**EXAMPLE 125**

35

**Preparation of 2-(5-Methoxy-5-oxopentylloxy)-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester**

Using the procedure of example 32, 2-(6-hydroxyhexyl)-6-(5-methoxy-5-oxopentylloxy)benzenepropanoic acid methyl ester was converted into 6-[6-[(methylsulfonyl)oxy]hexyl]-2-(5-methoxy-5-oxopentylloxy)benzenepropanoic acid methyl ester as an oil in quantitative yield.

**EXAMPLE 126****Preparation of 2-(4-Carboxybutoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid**

Using the procedure of example 11 and starting with 0.412 g (2.0 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 1.0 g (2.1 mmol) of 6-[6-[(methylsulfonyl)oxy]hexyl]-2-(5-methoxy-5-oxopentylloxy)benzenepropanoic acid methyl ester, 6-(5-methoxy-5-oxopentylloxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid methyl ester was obtained in 83% yield (0.97 g) as a colorless oil. This diester (1.7 mmol) was saponified with 5 ml of 3N aqueous lithium hydroxide solution in 40 ml of tetrahydrofuran at room temperature for 20 hr. Work-up as in example 4 gave an oily acid which was flash-chromatographed on silica gel eluting with 95:5:1 chloroform-methanol-acetic acid. There was obtained 0.76 g (81%) of pure 2-(4-carboxybutoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid. Recrystallization from hexane-ethyl acetate (2:1) gave 0.64 g (68%) of a colorless solid, mp 103-104 °.

Anal. Calcd. for  $C_{32}H_{42}O_8$ : C, 69.29; H, 7.63. Found: C, 69.22; H, 7.58 %.

**EXAMPLE 127****Preparation of 5-[(2-Oxo-2H-1-benzopyran-5-yl)oxy]pentanoic acid ethyl ester**

5 A mixture of 2.25 g (18.6 mmol) of 5-hydroxycoumarin, 4.2 g (20 mmol) of ethyl 5-bromovalerate, 7.0 g (50 mmol) of anhydrous granular potassium carbonate and 10 ml of dimethyl sulfoxide was stirred at room temperature for 24 hr. The resulting slurry was filtered with suction and the solids washed well with ethyl acetate. The filtrate and washes were combined and poured into water and the mixture was worked-up with ethyl acetate in the usual manner. The semi-solid residue was triturated and washed with hexane giving  
 10 2.36 g (44%) of 5-[(2-oxo-2H-1-benzopyran-5-yl)oxy]pentanoic acid ethyl ester as a tan solid.

**EXAMPLE 128****Preparation of (E)-5-[3-Hydroxy-2-(3-methoxy-3-oxo-1-propenyl)phenoxy]pentanoic acid methyl ester**

15 A solution of 2.36 g (8.15 mmol) of 5-[(2-oxo-2H-1-benzopyran-5-yl)oxy]pentanoic acid ethyl ester, 4.46 ml of 25% methanolic sodium methoxide and 15 ml of methanol was stirred and refluxed for 2 days and then concentrated under reduced pressure. The residue was treated with 1N hydrochloric acid and extracted with ethyl acetate. The combined ethyl acetate extracts were washed twice with saturated aqueous sodium bicarbonate solution and work-up was completed in the usual manner giving 1.1 g of a beige solid. This material was chromatographed on silica gel affording 0.93 g of (E)-5-[3-hydroxy-2-(3-methoxy-3-oxo-1-propenyl)phenoxy]pentanoic acid methyl ester as a colorless solid, mp 97-98 °. The aqueous alkaline washes were combined, acidified to pH 1 and worked-up with ethyl acetate in the usual  
 25 manner to give 1.4 g of brown, oily acidic material. This acid fraction was reesterified by refluxing in 30 ml of methanol containing 0.1 g of p-toluenesulfonic acid monohydrate for 24 hr. After concentration, usual work-up with ethyl acetate and chromatography an additional 0.9 g of the desired product was obtained (total yield: 1.83 g, 73%).

**EXAMPLE 129****Preparation of (E)-5-[3-[(Trifluoromethyl)sulfonyl]oxy]-2-(3-methoxy-3-oxo-1-propenyl)phenoxy]pentanoic acid methyl ester**

35 Using the procedure of example 119, (E)-5-[3-hydroxy-2-(3-methoxy-3-oxo-1-propenyl)phenoxy]pentanoic acid methyl ester (1.8 g; 5.83 mmol) was converted into (E)-5-[3-[(trifluoromethyl)sulfonyl]oxy]-2-(3-methoxy-3-oxo-1-propenyl)phenoxy]pentanoic acid methyl ester, a yellow oil, in 89% yield.

**EXAMPLE 130****Preparation of rac-(E)-5-[2-(3-Methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]pentanoic acid methyl ester**

45 A mixture of 2.27 g (5 mmol) of (E)-5-[3-[(trifluoromethyl)sulfonyl]oxy]-2-(3-methoxy-3-oxo-1-propenyl)phenoxy]pentanoic acid methyl ester, 1.0 g (5.5 mmol) of rac-6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexyne, 0.3 g (0.428 mmol) of dichlorobis(triphenylphosphine)palladium (II), 0.075 g of cuprous iodide, 7.5 ml of dry triethylamine, and 35 ml of dry N,N-dimethylformamide was stirred and heated at 100 ° for 3.5 hr. An additional 0.25 g of the acetylene was added and heating was continued for 24 hr at which point 0.75 g of the acetylene was added and heating was continued for 6 hr. The resulting mixture was cooled, poured into  
 50 water and worked-up with ethyl acetate in the usual manner. The crude oily product was chromatographed on silica gel. Elution with 10:1 toluene-ethyl acetate afforded 0.9 g (38%) of rac-(E)-5-[2-(3-methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]pentanoic acid methyl ester as a yellow oil.

55

**EXAMPLE 131**

**Preparation of rac-2-(5-Methoxy-5-oxopentyloxy)-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]-benzenepropanoic acid methyl ester**

A 0.9 g (1.9 mmol) sample of rac-(E)-5-[2-(3-methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]pentanoic acid methyl ester was hydrogenated in 60 ml of 1:1 methanol-ethyl acetate over 70 mg of 10% palladium on carbon at room temperature and 1 atmosphere. rac-2-(5-Methoxy-5-oxopentyloxy)-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester, an oil, was isolated by filtration of the catalyst and concentration of the filtrate in quantitative yield.

**EXAMPLE 132**

**Preparation of 2-(6-Hydroxyhexyl)-6-(5-methoxy-5-oxopentyloxy)benzenepropanoic acid methyl ester**

Using the procedure of example 52, rac-2-(5-methoxy-5-oxopentyloxy)-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester (0.98 g; 2.0 mmol) was converted into 2-(6-hydroxyhexyl)-6-(5-methoxy-5-oxopentyloxy)benzenepropanoic acid methyl ester, a colorless oil, in 83% yield. This material was identical to that produced as described in example 124.

**EXAMPLE 133**

**Preparation of (E)-4-[3-Hydroxy-4-(3-methoxy-3-oxo-1-propenyl)phenoxy]butanoic acid methyl ester**

Using the procedure of example 121, 4-[(2-oxo-2H-1-benzopyran-7-yl)oxy]butanoic acid ethyl ester was converted into (E)-4-[3-hydroxy-4-(3-methoxy-3-oxo-1-propenyl)phenoxy]butanoic acid methyl ester, a beige solid, mp 108-112 °, in 83 % yield.

**EXAMPLE 134**

**Preparation of (E)-4-[3-[(5-(Acetyloxy)pentyl)oxy]-4-(3-methoxy-3-oxo-1-propenyl)phenoxy]butanoic acid methyl ester**

Using the procedure of example 63 and starting with 2.01 g (6.84 mmol) of (E)-4-[3-hydroxy-4-(3-methoxy-3-oxo-1-propenyl)phenoxy]butanoic acid methyl ester and 1.57 g (7.51 mmol) of 5-bromopentyl acetate, (E)-4-[3-[(5-(acetyloxy)pentyl)oxy]-4-(3-methoxy-3-oxo-1-propenyl)phenoxy]butanoic acid methyl ester was obtained in quantitative yield as a pale-yellow oil.

**EXAMPLE 135**

**Preparation of (E)-4-[3-[(5-Hydroxypentyl)oxy]-4-(3-methoxy-3-oxo-1-propenyl)phenoxy]butanoic acid methyl ester**

A solution of 2.91 g (6.8 mmol) of (E)-4-[3-[(5-acetyloxy)pentyl]oxy]-4-(3-methoxy-3-oxo-1-propenyl)-phenoxy]butanoic acid methyl ester and 0.11 g of p-toluenesulfonic acid monohydrate in 60 ml of methanol was stirred and refluxed for 5 hr and then concentrated under reduced pressure. Treatment of the residue with water gave a solid which was filtered with suction, washed with water and dried under high vacuum giving 2.54 g of a solid. This material was chromatographed on 50 g of silica gel. Elution with 1:1 hexane-ethyl acetate afforded 2.04 g (78.5%) of (E)-4-[3-[(5-hydroxypentyl)oxy]-4-(3-methoxy-3-oxo-1-propenyl)-phenoxy]butanoic acid methyl ester as a colorless solid.

**EXAMPLE 136****Preparation of 2-[(5-Hydroxypentyl)oxy]-4-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester**

5

A 2.0 g (5.26 mmol) sample of (E)-4-[3-[(5-hydroxypentyl)oxy]-4-(3-methoxy-3-oxo-1-propenyl)phenoxy]-butanoic acid methyl ester was hydrogenated in 100 ml of 1:1 methanol-ethyl acetate over 0.1 g of 10% palladium on carbon at room temperature and 1 atmosphere. 2-[(5-Hydroxypentyl)oxy]-4-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester, an oil, was isolated by filtration of the catalyst and concentration of the filtrate in quantitative yield.

10

**EXAMPLE 137****Preparation of 2-[5-[(Methylsulfonyl)oxy]pentyl]oxy]-4-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester**

15

Using the procedure of example 32, the 2-[(5-hydroxypentyl)oxy]-4-(4-methoxy-4-oxobutoxy)-benzenepropanoic acid methyl ester from the preceding example (2.0 g; 5.23 mmol) was converted into 2-[5-[(methylsulfonyl)oxy]pentyl]oxy]-4-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester in essentially quantitative yield and was used without further purification.

20

**EXAMPLE 138****Preparation of 4-(3-Carboxypropoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid**

25

Using the procedure of example 11 and starting with 0.28 g (1.4 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.65 g (1.41 mmol) of 2-[5-[(methylsulfonyl)oxy]pentyl]oxy]-4-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester, 4-(4-methoxy-4-oxobutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid methyl ester was obtained in 75% yield (0.6 g) as a solid, mp 58-59 °. This diester (1.05 mmol) was saponified with 3 ml of 3N aqueous lithium hydroxide solution in 30 ml of tetrahydrofuran at room temperature for 16 hr. Work-up as in example 4 but using dichloromethane rather than ether gave a solid acid which was flash-chromatographed on silica gel eluting with 95:5:1 chloroform:methanol:acetic acid. Recrystallization from ethyl acetate gave 0.44 g (78%) of pure 4-(3-carboxypropoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid as a colorless solid, mp 163-164 °.

30

35

Anal. Calcd. for  $C_{30}H_{38}O_9$ : C, 66.40; H, 7.06. Found: C, 66.63; H, 7.05 %.

**EXAMPLE 139**

40

**Preparation of 3-(3-Ethoxy-3-oxopropyl)-4-methoxy- $\delta$ -oxobenzenepentanoic acid**

A mixture of 10.61 g (50.95 mmol) of 2-methoxybenzenepropanoic acid ethyl ester, 9.30 g (81.51 mmol) of glutaric anhydride, 20.89 g (0.157 mol) of aluminum chloride and 100 ml of anhydrous methylene chloride was stirred and heated in an oil bath kept at 46 ° for 16.5 hr. The temperature of the oil bath was raised to 80 ° and stirring was continued for another 3 hr. After being cooled to room temperature, the mixture was poured onto crushed ice. To this was added 200 ml of water and 200 ml of 6N hydrochloric acid solution and most of the organic solvents were removed under aspirator pressure. The residue was extracted 3 times with ethyl acetate and the combined ethyl acetate extract was washed once with 3N sulfuric acid solution, once with water, and finally, 3 times with saturated sodium carbonate solution. The combined sodium carbonate solution was back extracted once with ether (which was discarded) and then cooled in an ice bath. To this cold, alkaline solution was slowly added concentrated hydrochloric acid solution. The precipitate was collected by filtration to give 12.14 g (73.9%) of a light-beige solid. An analytical sample was obtained by recrystallization from ethanol to give the title compound as colorless needles, mp 124-126 °.

50

55

Anal. Calcd. for  $C_{17}H_{22}O_6$ : C, 63.34; H, 6.88. Found: C, 63.66; H, 6.96 %.

**EXAMPLE 140****Preparation of 3-(3-Ethoxy-3-oxopropyl)-4-hydroxy- $\delta$ -oxobenzenepentanoic acid ethyl ester**

- 5 A mixture of 1.61 g (5.0 mmol) of 3-(3-ethoxy-3-oxopropyl)-4-methoxy- $\delta$ -oxobenzenepentanoic acid and 11.56 g (0.1 mol) of pyridine hydrochloride was heated at ca. 240 ° for 1.33hr. After being cooled to room temperature, the reaction mixture was treated with 100 ml of water and extracted twice with ether and once with ethyl acetate. The organic extracts were processed in the usual manner to give 1.30 g of a tan solid which was dissolved in 120 ml of ethanol. To this solution was slowly added 30 drops of thionyl chloride.
- 10 The resulting solution was heated at reflux for 7 hr and then kept at room temperature for ca. 65 hr. The solvent was removed in vacuo and the residue was purified by flash chromatography on 100 g of silica gel eluting with 3:1 hexane-ethyl acetate to give 1.44 g (85.6%) of the title compound as a light-tan solid, mp 68-69 °.

Anal. Calcd. for  $C_{18}H_{24}O_6$ : C, 64.27; H, 7.19. Found: C, 64.39; H, 7.31 %.

15

**EXAMPLE 141****Preparation of 3-(3-Ethoxy-3-oxopropyl)-4-methoxy- $\gamma$ -oxobenzenebutanoic acid**

- 20 Starting with a mixture of 3.12 g (15.0 mmol) of 2-methoxybenzenepropanoic acid ethyl ester, 1.53 g (15.3 mmol) of succinic anhydride, 4.46 g (33.5 mmol) of aluminum chloride and 20 ml of methylene chloride, the title compound (3.59 g, 77.7%) was obtained as a white solid, mp 128-129 ° (recrystallized from ethanol), using the procedure of example 139.

Anal. Calcd. for  $C_{16}H_{20}O_6$ : C, 62.33; H, 6.54. Found: C, 62.50; H, 6.61 %.

25

**EXAMPLE 142****Preparation of 3-(3-Ethoxy-3-oxopropyl)-4-hydroxy- $\gamma$ -oxobenzenebutanoic acid ethyl ester**

- 30 Starting with a mixture of 6.48 g (21.0 mmol) of 3-(3-ethoxy-3-oxopropyl)-4-methoxy- $\gamma$ -oxobenzenebutanoic acid and 24.4 g (0.211 mol) of pyridine hydrochloride, the title compound (2.87 g, 42.4%) was obtained as a light-tan oil using the procedure of example 140.

Anal. Calcd. for  $C_{17}H_{22}O_6$ : C, 63.34; H, 6.88. Found: C, 63.03; H, 6.84 %.

**EXAMPLE 143****Preparation of 5-[[4-(Ethoxycarbonyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester**

- A mixture of 3.6 g (20 mmol) of 4-carboxybenzoic acid methyl ester, 25 ml of toluene and 6 ml of thionyl chloride was heated in an oil bath kept at ca. 90 °. Another 25 ml of toluene was added after 1 hr, an additional 6 ml quantity of thionyl chloride was added after 2.3 hr, and heating was continued for an additional 25 hr. The solvent and excess thionyl chloride were removed in vacuo. To the residue were added 25 ml of toluene and 6 ml of thionyl chloride and the mixture was again heated at 95 ° for 0.5 hr and then at 45 ° for 64 hr and finally at 90 ° for 3 hr. The solvent and excess thionyl chloride were again removed in vacuo. This crude acid chloride was mixed with 4.16 g (20 mmol) of 2-methoxybenzenepropanoic acid ethyl ester and 45 ml of methylene chloride. 10.7 g (80 mmol) of aluminium chloride were added in one portion and the resulting mixture was heated in an oil bath kept at 45 ° for 18 hr and then at 75 ° for 3.5 hr. After being cooled to room temperature, the mixture was poured onto crushed ice and 75 ml of 3N sulfuric acid solution was added. The resulting mixture was worked-up with ether in the usual manner. The residue was dissolved in 200 ml of ethanol. Concentrated sulfuric acid (5 ml) was added and the solution was heated under reflux for 5.8 hr. Most ethanol was removed under aspirator pressure and the residue was worked-up with ethyl acetate as usual. The crude product was purified by flash chromatography on 700 g of silica gel eluting with 3:1 hexane-ethyl acetate and afforded 2.0 g (27.1%) of the title compound as an off-white solid, mp 70-71 °.

55

Anal. Calcd. for  $C_{21}H_{22}O_6$ : C, 68.10; H, 5.99. Found: C, 68.07; H, 6.16 %.

Further elution gave 1.325 g of a mixture of the title compound and 5-[[4-(methoxycarbonyl)phenyl]carbonyl]-2-hydroxybenzenepropanoic acid ethyl ester.



**EXAMPLE 144****Preparation of 2-[(5-Bromopentyl)oxy]benzenebutanoic acid methyl ester**

5 Using the procedure of example 108, 2-hydroxybenzenebutanoic acid methyl ester was converted into the title compound by alkylation with 1,5-dibromopentane in 81% yield as a colorless oil.

**EXAMPLE 145**

10 **Preparation of 2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenebutanoic acid**

Using the procedure of example 4, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one was converted into the title compound by alkylation with 2-[(5-bromopentyl)oxy]benzenebutanoic acid methyl ester from the preceding example followed by saponification in 46.5% overall yield. The product was an off-white solid, mp 116-118 °, recrystallized from acetonitrile.

Anal. Calcd. for C<sub>27</sub>H<sub>34</sub>O<sub>6</sub>: C, 71.34; H, 7.54. Found: C, 71.23; H, 7.62 %.

**EXAMPLE 146**

20 **Preparation of 2-[(5-Bromopentyl)oxy]benzenepentanoic acid methyl ester**

Using the procedure of example 108, 2-hydroxybenzenepentanoic acid methyl ester was converted into the title compound in 78% yield as a colorless oil.

25 **EXAMPLE 147**

30 **Preparation of 2-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepentanoic acid**

Using the procedure of example 4, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one was converted into the title compound by alkylation with 2-[(5-bromopentyl)oxy]benzenepentanoic acid methyl ester from the preceding example, followed by saponification in 46.5% overall yield. The product was an off-white solid, mp 75-76 °, recrystallized from hexane-ethyl acetate.

35 Anal. Calcd. for C<sub>28</sub>H<sub>36</sub>O<sub>6</sub>: C, 71.77; H, 7.74. Found: C, 71.83; H, 7.93 %.

**EXAMPLE 148**

40 **Preparation of rac-(E)-3-[2-(2-Methoxy-2-oxoethoxy)]-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]-phenyl]-2-propenoic acid methyl ester**

Using the procedure of example 122, rac-(E)-3-[2-hydroxy-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-2-propenoic acid methyl ester (example 121) was alkylated with methyl bromoacetate giving the title compound in 75% yield as a colorless oil.

45 **EXAMPLE 149**

50 **Preparation of rac-2-(2-Methoxy-2-oxoethoxy)-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]-benzenepropanoic acid methyl ester**

Using the procedure of example 123, rac-(E)-3-[2-(2-methoxy-2-oxoethoxy)]-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-2-propenoic acid methyl ester from the preceding example was catalytically hydrogenated giving the title compound in quantitative yield as a colorless oil.

55

**EXAMPLE 150****Preparation of 2-(6-Hydroxyhexyl)-6-(2-methoxy-2-oxoethoxy)benzenepropanoic acid methyl ester**

5 Using the procedure of example 52, rac-2-(2-methoxy-2-oxoethoxy)-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-hexyl]benzenepropanoic acid methyl ester from the preceding example was converted to the title compound in 41.3% yield as a colorless oil.

**EXAMPLE 151**

10 **Preparation of 2-(2-Methoxy-2-oxoethoxy)-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester**

Using the procedure of example 32, 2-(6-hydroxyhexyl)-6-(2-methoxy-2-oxoethoxy)benzenepropanoic acid methyl ester from the preceding experiment was converted into the title compound, a yellow oil, in 91% yield.

**EXAMPLE 152**

20 **Preparation of 2-(Carboxymethoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]-hexyl]benzenepropanoic acid**

Using the procedure of example 126, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one was converted into the title compound by alkylation with 2-(2-methoxy-2-oxoethoxy)-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example, followed by saponification in 64.4% overall yield. The product was an off-white solid, mp 127-129 °, recrystallized from hexane-ethyl acetate.

Anal. Calcd. for C<sub>29</sub>H<sub>36</sub>O<sub>8</sub>: C, 67.95; H, 7.08. Found: C, 67.75; H, 7.18 %.

**EXAMPLE 153**

30 **Preparation of rac-(E)-6-[2-(3-Methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]hexanoic acid ethyl ester**

Using the procedure of example 122, rac-(E)-3-[2-hydroxy-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-2-propenoic acid methyl ester (example 121) was alkylated with ethyl 6-bromohexanoate giving the title compound as a pale-yellow oil in 93.3% yield.

**EXAMPLE 154**

40 **Preparation of rac-2-[(6-Ethoxy-6-oxohexyl)oxy]-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester**

Using the procedure of example 123, rac-E-6-[2-(3-methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]hexanoic acid ethyl ester from the preceding example was catalytically hydrogenated giving the title compound as an oil in quantitative yield.

**EXAMPLE 155**

50 **Preparation of 2-(6-Hydroxyhexyl)-6-[(6-methoxy-6-oxohexyl)oxy]-benzenepropanoic acid methyl ester**

Using the procedure of example 52, rac-2-[(6-ethoxy-6-oxohexyl)oxy]-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester was converted to the title compound, a colorless oil, in 90% yield.

55

**EXAMPLE 156****Preparation of 2-[(6-Methoxy-6-oxohexyl)oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester**

Using the procedure of example 32, 2-(6-hydroxyhexyl)-6-[(6-methoxy-6-oxohexyl)oxy]-benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, an oil, in quantitative yield.

**EXAMPLE 157****Preparation of 2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid**

Using the procedure of example 126, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one was converted into the title compound by alkylation with 2-[(6-methoxy-6-oxohexyl)oxy]-6-[6-(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example, followed by saponification in 79% overall yield. The product was a colorless solid, mp 86-88 °, recrystallized from hexane-ethyl acetate.

Anal. Calcd. for C<sub>33</sub>H<sub>44</sub>O<sub>8</sub>: C, 69.70; H, 7.80. Found: C, 69.78; H, 7.83 %.

**EXAMPLE 158****Preparation of (E,E)-3,3'-(4-Hydroxy-1,3-phenylene)bis-2-propenoic acid dimethyl ester**

A mixture of 5.0 g (33.3 mmol) of 5-formylsalicylaldehyde and 24.5 g (73.3 mmol) of methyl (triphenylphosphoranylidene)acetate in 150 ml of toluene was stirred and refluxed for 2.5 hr and then kept at room temperature overnight. The solvent was removed in vacuo and the solid residue was flash-chromatographed on silica gel. There was obtained 8.07 g (92.5%) of the title compound as a colorless solid.

**EXAMPLE 159****Preparation of (E,E)-3,3'-[4-[[5-(Acetyloxy)pentyl]oxy]-1,3-phenylene]- bis-2-propenoic acid dimethyl ester**

Using the procedure of example 63, (E,E)-3,3'-(4-hydroxy-1,3-phenylene)bis-2-propenoic acid dimethyl ester from the preceding example was converted into the title compound, a solid, in 85% yield.

**EXAMPLE 160****Preparation of 4-[[5-(Acetyloxy)pentyl]oxy]-1,3-benzenedipropenoic acid dimethyl ester**

Catalytic hydrogenation of 10.17 g (26.04 mmol) of (E,E)-3,3'-[4-[[5-(acetyloxy)pentyl]oxy]-1,3-phenylene]bis-2-propenoic acid dimethyl ester from the preceding example was carried out using 2.03 g of 10% palladium on carbon in 125 ml of dry tetrahydrofuran at room temperature and 1 atmosphere. After filtration of the catalyst and concentration of the filtrate the title compound was obtained in quantitative yield as a pale-yellow oil.

**EXAMPLE 161****Preparation of 4-[[5-Hydroxypentyl]oxy]-1,3-benzenedipropenoic acid dimethyl ester**

Using the procedure of example 135, 4-[[5-(acetyloxy)pentyl]oxy]-1,3-benzene-dipropenoic acid dimethyl ester from the preceding example was converted into the title compound, a pale-yellow oil, in 93.5% yield.

**EXAMPLE 162****Preparation of 4-[[5-[(Methylsulfonyl)oxy]pentyl]oxy]-1,3-benzene-dipropanoic acid dimethyl ester**

Using the procedure of example 32, 4-[(5-hydroxypentyl)oxy]-1,3-benzene-dipropanoic acid dimethyl ester from the preceding example was converted into the title compound, a light-tan oil, in quantitative yield.

**EXAMPLE 163****Preparation of 4-[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-1,3-benzenedipropanoic acid**

Using the procedure of example 126, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one was converted into the title compound by alkylation with 4-[5-(methylsulfonyl)oxypentyl]oxy]-1,3-benzenedipropanoic acid methyl ester from the preceding example, followed by saponification in 8% overall yield. The product was a colorless solid, mp 108-109 °, recrystallized from hexane-ethyl acetate.

Anal. Calcd. for  $C_{29}H_{36}O_8$ : C, 66.72; H, 6.97. Found: C, 66.49; H, 7.05 %.

**EXAMPLE 164****Preparation of rac-(E)-3-[2-[6-[(Tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]-6-[[trifluoromethyl)sulfonyl]oxy]phenyl]-2-propenoic acid methyl ester**

Using the procedure of example 119, rac-(E)-3-[2-hydroxy-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-2-propenoic acid methyl ester from example 121 was converted into the title compound, a tan oil, in quantitative yield.

**EXAMPLE 165****Preparation of rac-(E)-6-[2-(3-Methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-5-hexynoic acid methyl ester**

Using the procedure of example 130, rac-(E)-3-[2-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]-6-[[trifluoromethyl)sulfonyl]oxy]phenyl]-2-propenoic acid methyl ester from the preceding example was converted into the title compound, a tan oil, by reaction with methyl 5-hexynoate in 68.3% yield.

**EXAMPLE 166****Preparation of rac-2-(3-Methoxy-3-oxopropyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]-benzenehexanoic acid methyl ester**

Rac-(E)-6-[2-(3-methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-5-hexynoic acid methyl ester from the preceding example was catalytically hydrogenated over 10% palladium on carbon in methanol at room temperature and 1 atmosphere. The title compound was obtained in 97% yield as a pale-yellow oil.

**EXAMPLE 167****Preparation of 3-(6-Hydroxyhexyl)-2-(3-methoxy-3-oxopropyl)benzenehexanoic acid methyl ester**

Using the procedure of example 52, rac-2-(3-methoxy-3-oxopropyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenehexanoic acid methyl ester from the preceding example was converted into the title compound, a pale-yellow oil, in 88.4% yield.

**EXAMPLE 168**

**Preparation of 2-(3-Methoxy-3-oxopropyl)-3-[6-[(methylsulfonyl)oxy]hexyl]benzenehexanoic acid methyl ester**

5

Using the procedure of example 32, 3-(6-hydroxyhexyl)-2-(3-methoxy-3-oxo-propyl)benzenehexanoic acid methyl ester from the preceding example was converted to the title compound, a oil, in quantitative yield.

10 **EXAMPLE 169**

**Preparation of 2-(2-Carboxyethyl)-3-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenehexanoic acid**

15

Using the procedure of example 126, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one was converted into the nine compound by alkylation with 2-(3-methoxy-3-oxopropyl)-3-[6-(methylsulfonyl)oxy]hexyl]-benzenehexanoic acid methyl ester from the preceding example, followed by saponification in 16.8% overall yield. The product was a colorless solid, mp 109-110 °, recrystallized from acetonitrile.

Anal. Calcd. for C<sub>33</sub>H<sub>44</sub>O<sub>7</sub>: C, 71.71; H, 8.02. Found: C, 71.80; H, 7.84%.

20

**EXAMPLE 170**

**Preparation of rac-(E)-5-[2-(3-Methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]-2,2-dimethylpentanoic acid methyl ester**

25

Using the procedure of example 122, rac-(E)-3-[2-hydroxy-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-2-propenoic acid methyl ester (example 121) was alkylated with methyl 5-bromo-2,2-dimethylpentanoate giving the title compound in 92% yield as a colorless oil.

30 **EXAMPLE 171**

**Preparation of rac-2-[(5-Methoxy-4,4-dimethyl-5-oxopentyl)oxy]-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester**

35

Using the procedure of example 123, rac-(E)-5-[2-(3-methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]-2,2-dimethylpentanoic acid methyl ester from the preceding example was catalytically hydrogenated giving the title compound as a oil in quantitative yield.

**EXAMPLE 172**

40

**Preparation of 2-(6-Hydroxyhexyl)-6-[(5-methoxy-4,4-dimethyl-5-oxopentyl)oxy]benzenepropanoic acid methyl ester**

Using the procedure of example 52, rac-2-[(5-methoxy-4,4-dimethyl-5-oxopentyl)oxy]-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, a colorless oil, in 88% yield.

**EXAMPLE 173**

**Preparation of 2-[(5-Methoxy-4,4-dimethyl-5-oxopentyl)oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]-benzenepropanoic acid methyl ester**

Using the procedure of example 32, 2-(6-hydroxyhexyl)-6-[(5-methoxy-4,4-dimethyl-5-oxopentyl)oxy]-benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, a colorless oil, in 95% yield.

55

**EXAMPLE 174****Preparation of 2-[(4-Carboxy-4-methylpentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid**

Using the procedure of example 126, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one was converted into the title compound by alkylation with 2-[(5-methoxy-4,4-dimethyl-5-oxopentyl)oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example, followed by saponification in 33.9% overall yield. The product was a colorless solid, mp 85-87 °, recrystallized from hexane-ethyl acetate.

Anal. Calcd. for C<sub>34</sub>H<sub>46</sub>O<sub>8</sub>: C, 70.08; H, 7.96. Found: C, 70.07; H, 8.03 %.

**EXAMPLE 175****Preparation of 5-[6-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-hexynyl]-2H-1-benzopyran-2-one**

Using the procedure of example 120, trifluoromethanesulfonic acid 2-oxo-2H-1-benzopyran-5-yl ester from example 119 was converted to the title compound by reaction with (1,1-dimethylethyl)(5-hexynyloxy)-dimethylsilane. The product was a solid obtained in 87% yield.

**EXAMPLE 176****Preparation of (E)-3-[2-Hydroxy-6-(6-hydroxy-1-hexynyl)phenyl]-2-propenoic acid methyl ester**

Using the procedure of example 121, 5-[6-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-hexynyl]-2H-1-benzopyran-2-one from the preceding example was converted into the title compound, a solid, in 56% yield.

**EXAMPLE 177****Preparation of (E)-3-[2-[[5-(Acetyloxy)pentyl]oxy]-6-(6-hydroxy-1-hexynyl)phenyl]-2-propenoic acid methyl ester**

Using the procedure of example 63, (E)-3-[2-hydroxy-6-(6-hydroxy-1-hexynyl)phenyl]-2-propenoic acid methyl ester from the preceding example was converted into the title compound by alkylation with 5-bromopentylacetate. The product was obtained as a colorless oil in 77% yield.

**EXAMPLE 178****Preparation of 2-[[5-(Acetyloxy)pentyl]oxy]-6-(6-hydroxyhexyl)benzenepropanoic acid methyl ester**

Using the procedure of example 123, (E)-3-[2-[[5-(acetyloxy)pentyl]oxy]-6-(6-hydroxy-1-hexynyl)phenyl]-2-propenoic acid methyl ester from the preceding example was converted into the title compound by catalytic hydrogenation. The product was obtained in quantitative yield as a colorless oil.

**EXAMPLE 179****Preparation of 2-[[5-(Acetyloxy)pentyl]oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester**

Using the procedure of example 32, 2-[5-[(acetyloxy)pentyl]oxy]-6-(6-hydroxyhexyl)benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, a oil, in 62% yield after flash-chromatographic purification.

**EXAMPLE 180****Preparation of 2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-6-[(5-hydroxypentyl)oxy]benzenepropanoic acid**

Using the procedure of example 126, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one was converted into the title compound by alkylation with 2-[5-[(acetyloxy)pentyl]oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example, followed by saponification in 57.4% overall yield. The product was a colorless solid, mp 102-103 °, recrystallized from hexane-ethyl acetate.

Anal. Calcd. for C<sub>32</sub>H<sub>44</sub>O<sub>7</sub>: C, 71.08; H, 8.20. Found: C, 70.92; H, 8.26 %.

**EXAMPLE 181****Preparation of (E)-8-[2-(3-Methoxy-3-oxo-1-propenyl)-3-(6-hydroxy-1-hexynyl)phenoxy]octanoic acid methyl ester**

Using the procedure of example 122, (E)-3-[2-hydroxy-6-(6-hydroxy-1-hexynyl)phenyl]-2-propenoic acid methyl ester (example 176) was alkylated with methyl 8-bromooctanoate giving the title compound in 67% yield as a colorless oil.

**EXAMPLE 182****Preparation of 2-(6-Hydroxyhexyl)-6-[(8-methoxy-8-oxooctyl)oxy]benzenepropanoic acid methyl ester**

Using the procedure of example 123, (E)-8-[2-(3-methoxy-3-oxo-1-propenyl)-3-(6-hydroxy-1-hexynyl)phenoxy]octanoic acid methyl ester from the preceding example was converted into the title compound by catalytic hydrogenation. The product was obtained in quantitative yield as a colorless oil.

**EXAMPLE 183****Preparation of 2-[(8-Methoxy-8-oxooctyl)oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester**

Using the procedure of example 32, 2-(6-hydroxyhexyl)-6-[(8-methoxy-8-oxooctyl)oxy]benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, a pale-yellow oil, in quantitative yield.

**EXAMPLE 184****Preparation of 2-[(7-Carboxyheptyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid**

A mixture of 0.68 g (1.3 mmol) of 2-[(8-methoxy-8-oxooctyl)oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example, 0.24 g (1.17 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one, 0.26 g (1.88 mmol) of anhydrous granular potassium carbonate, 0.215 g (1.43 mmol) of anhydrous sodium iodide and 10 ml of dry acetonitrile was stirred and refluxed for 24 hr. After being cooled, the reaction mixture was poured onto ice-water and worked-up with ether in the usual manner. The crude product was flash-chromatographed on silica gel eluting with 2:1 hexane-ethyl acetate. There was obtained 0.69 g (94.5%) of 2-[(8-methoxy-8-oxooctyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid methyl ester as a colorless oil. A solution of this diester and 2.5 ml of 3N aqueous lithium hydroxide solution in 15 ml of tetrahydrofuran was stirred at room temperature for 24 hr. The solvent was removed under reduced pressure and the residue was dissolved in water. The resulting solution was extracted with ether (the extracts were discarded) and then acidified with 3N aqueous hydrochloric acid. Work-up with ether in the usual manner gave a oily acid product which was flash-chromatographed on silica gel eluting with 90:10:1 chloroform-methanol-acetic acid. Recrystallization of the pure acid from hexane-ethyl acetate afforded 0.5 g (76%) of the title compound as a colorless solid, mp 79-81 °.

Anal. Calcd. for  $C_{35}H_{48}O_8$ : C, 70.44; H, 8.11. Found: C, 70.33; H, 8.20 %.

**EXAMPLE 185**

5 **Preparation of (E)-9-[3-(6-Hydroxy-1-hexynyl)-2-(3-methoxy-3-oxo-1-propenyl)phenoxy]nonanoic acid methyl ester**

Using the procedure of example 122, (E)-3-[2-hydroxy-6-(6-hydroxy-1-hexynyl)phenyl]-2-propenoic acid methyl ester (example 176) was alkylated with methyl 9-bromo-nonanoate giving the title compound in 71%  
10 yield as a colorless oil.

**EXAMPLE 186**

15 **Preparation of 2-(6-Hydroxyhexyl)-6-[(9-methoxy-9-oxononyl)oxy]benzenepropanoic acid methyl ester**

Using the procedure of example 123, (E)-9-[3-(6-hydroxy-1-hexynyl)-2-(3-methoxy-3-oxo-1-propenyl)-phenoxy]nonanoic acid methyl ester from the preceding example was converted into the title compound by catalytic hydrogenation. The product was obtained in quantitative yield as a colorless oil.

**EXAMPLE 187**

25 **Preparation of 2-[(9-Methoxy-9-oxononyl)oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester**

Using the procedure of example 32, 2-(6-hydroxyhexyl)-6-[(9-methoxy-9-oxo-nonyl)oxy]-benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, a pale-yellow oil, in quantitative yield.

30 **EXAMPLE 188**

**Preparation of 2-[(8-Carboxyoctyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]-hexyl]benzenepropanoic acid**

35 Using the procedure of example 184, the title compound was prepared in 47% overall yield by alkylation of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one with 2-[(9-methoxy-9-oxononyl)oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example followed by saponification. The diacid product was a colorless solid, mp 63-65°, recrystallized from hexane-ethyl acetate.

40 Anal. Calcd. for  $C_{36}H_{50}O_8$ : C, 70.79; H, 8.25. Found: C, 71.02; H, 8.40 %.

**EXAMPLE 189**

45 **Preparation of 1,3-Dimethoxy-2-(3-phenylpropyl)benzene**

A solution of 8.70 g (63 mmol) of 1,3-dimethoxybenzene in 164 ml of anhydrous tetrahydrofuran was stirred at -20 ° while 1.6M n-butyllithium in hexane (42.1 ml; 67.2 mmol) was added dropwise, over 20 min. The solution was stirred at -20 ° for 3 hr and then allowed to warm to -5 ° whereupon 15.66 g (63.6 mmol) of 1-iodo-3-phenylpropane was added over 15 min. The reaction mixture was stirred at -5 ° for 1 hr and  
50 then at room temperature for 3 days. After being recooled to -5 °, the reaction mixture was decomposed by the addition of 1.5N aqueous sulfuric acid. Water was added and the mixture was worked-up with ether in the usual manner. The residue was treated with 100 ml of hexane and the mixture was filtered. Removal of the solvent in vacuo gave 15.28 g (94.7%) of the title compound as a yellow oil.

55



**EXAMPLE 190****Preparation of 1-[2,4-Dimethoxy-3-(3-phenylpropyl)phenyl]ethanone**

5 A solution of 15.28 g (59.6 mmol) of 1,3-methoxy-2-(3-phenylpropyl)benzene from the preceding example ad 4.68 g (59.6 mmol) of acetyl chloride in 306 ml of dichloromethane was stirred at -5 to 0 ° and 7.95 g (59.6 mmol) of aluminum chloride was added. The resulting mixture was stirred at -5 to 0 ° for 2 hr and then allowed to warm to room temperature before being poured onto ice. Work-up with ether in the usual manner gave a product which was chromatographed on silica gel. Elution with 7:3 hexane-ether  
 10 afforded 10.0 g (56.3%) of the title compound as a pale-yellow oil.

**EXAMPLE 191****Preparation of 1-[2,4-Dihydroxy-3-(3-phenylpropyl)phenyl]ethanone**

15 A solution of 10.0 g (33.5 mmol) of 1-[2,4-dimethoxy-3-(3-phenylpropyl)phenyl]ethanone from the preceding example in 250 ml of dichloromethane was stirred at -50 ° while 67 ml (67 mmol) of 1M boron tribromide in dichloromethane was added over a 15 min period. The reaction mixture was stirred at -50 ° for 1 hr and at room temperature for 3 days before being poured onto ice. Work-up with 9:1  
 20 dichloromethane-methanol in the usual manner gave a product which was chromatographed on silica gel. Elution with hexane-ether mixtures gave 6.69 g (74%) of the title compound as a solid. Recrystallization of a sample from ether-hexane gave colorless solid, mp 120-122 °.

Anal. Calcd. for  $C_{17}H_{18}O_3$ : C, 75.53; H, 6.71. Found: C, 75.31; H, 6.73 %.

**EXAMPLE 192****Preparation of 1-[2-Hydroxy-4-(phenylmethoxy)-3-(3-phenylpropyl)phenyl]ethanone**

30 A mixture of 6.69 g (24.7 mmol) of 1-[2,4-hydroxy-3-(3-phenylpropyl)phenyl]ethanone from the preceding example, 5.35 g (31.3 mmol) of benzyl bromide, 14.9 g (0.108 mol) of anhydrous potassium carbonate, 115 ml of dry N,N-dimethylformamide ad 230 ml of acetone was stirred and refluxed for 8 hr. After being cooled, the slurry was filtered with suction ad the solids washed well with acetone. The filtrate ad washes were combined ad concentrated under reduced pressure to give a yellow oil which was chromatographed on silica gel. There was obtained 5.57 g (62.6%) of the desired monoether as a pale-yellow solid. Recrystallization of a sample from hexane-ethyl acetate gave the title compound as colorless needles, mp 115-116 °.  
 35

Anal. Calcd. for  $C_{24}H_{24}O_3$ : C, 79.97; H, 6.71. Found: C, 79.97; H, 6.80 %.

**EXAMPLE 193****Preparation of 7-(Phenylmethoxy)-8-(3-phenylpropyl)-4H-1-benzopyran-4-one**

40 Using the procedure of example 1, 1-[2-hydroxy-4-(phenylmethoxy)-3-(3-phenylpropyl)phenyl]ethanone from the preceding example was converted into the title compound, a colorless solid, mp 106-107.5 ° (recrystallized from hexane-ethyl acetate), in 56.7% yield.

45 Anal. Calcd. for  $C_{25}H_{22}O_3$ : C, 81.05; H, 5.99. Found: C, 81.20; H, 5.99 %.

**EXAMPLE 194****Preparation of 2,3-Dihydro-7-hydroxy-8-(3-phenylpropyl)-4H-1-benzopyran-4-one**

50 Catalytic hydrogenation of 7-(phenylmethoxy)-8-(3-phenylpropyl)-4H-1-benzopyran-4-one from the preceding example using the procedure of example 2 gave the title compound, a colorless solid, mp 110-112 ° (recrystallized from hexane-ether), in 44.9% yield.

Anal. Calcd. for  $C_{18}H_{18}O_3$ : C, 76.57; H, 6.43. Found: C, 76.42; H, 6.43 %.

55

**EXAMPLE 195****Preparation of 2-[[5-[[3,4-Dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl]oxy]pentyl]oxy]-benzenepropanoic acid**

Using the procedure of example 11 and starting with 1.13 g (4 mmol) of 2,3-dihydro-7-hydroxy-8-(3-phenylpropyl)-4H-1-benzopyran-4-one and 1.38 g (4 mmol) of 2-[[5-[(methylsulfonyl)oxy]pentyl]oxy]-benzenepropanoic acid methyl ester, 2-[[5-[[3,4-dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl]oxy]pentyl]oxy]benzenepropanoic acid methyl ester was obtained in 75.5% yield (1.6 g) as a pale-yellow oil. This diester (3 mmol) was saponified with 13.6 ml of 3N aqueous lithium hydroxide solution in 80 ml of tetrahydrofuran at room temperature for 96 hr. Work-up as in example 4 and recrystallization from ethyl acetate gave 0.6 g (38.5%) of the title acid, a colorless solid, mp 98-99°.

Anal. Calcd. for  $C_{32}H_{36}O_6$ : C, 74.40; H, 7.02. Found: C, 74.47; H, 6.86 %.

**EXAMPLE 196****Preparation of 2-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-6-[[5-(dimethylamino)-5-oxopentyl]oxy]-N,N-dimethylbenzenepropanamide**

A solution of 0.555 g (1.0 mmol) of 2-(4-carboxybutoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid from example 126, 0.196 g (2.4 mmol) of dimethylamine hydrochloride, 0.334 g (2.4 mmol) of 1-hydroxybenzotriazole, 0.48 g (2.5 mmol) of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, 0.34 ml (2.4 mmol) of triethylamine and 10 ml of dichloromethane was stirred overnight at room temperature. The reaction mixture was poured into 1N hydrochloric acid and worked-up with dichloromethane in the usual manner. The crude product was flash-chromatographed on silica gel eluting with 98:1:1 chloroform-methanol-acetic acid. There was obtained 0.3 g (49%) of the title diamide as a colorless, viscous oil.

Anal. Calcd. for  $C_{36}H_{52}N_2O_6$ : C, 71.02; H, 8.61; N, 4.60. Found: C, 70.89; H, 8.67; N, 4.50 %.

**EXAMPLE 197****Preparation of 2-[6-[4-Acetyl-3-hydroxy-2-(3-phenylpropyl)phenoxy]hexyl]-6-[(6-methoxy-6-oxohexyl)oxy]benzenepropanoic acid methyl ester**

A mixture of 0.81 g (3 mmol) of 1-[2,4-dihydroxy-3-(3-phenylpropyl)phenyl]ethanone from example 191, 1.6 g (3.29 mmol) of 2-[(6-methoxy-6-oxohexyl)oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester from example 156, 0.66 g (4.78 mmol) of anhydrous granular potassium carbonate, 0.55 g (3.67 mmol) of sodium iodide and 25 ml of acetonitrile was stirred and refluxed for 18.5 hr. The resulting thick slurry was cooled, diluted with ether and washed with water, 12% aqueous sodium bisulfite solution and brine, and work-up was completed in the usual manner. Thin layer chromatographic analysis of the oily product revealed that alkylation was incomplete. Therefore, the product was dissolved in 5 ml of acetonitrile and 0.69 g (5 mmol) of anhydrous granular potassium carbonate was added. The resulting mixture was stirred and refluxed for 24 hr before being worked-up as described above. The oily product (2.01 g) was chromatographed on 50 g of silica gel. Elution with 1:1 hexane-ether afforded 1.80 g (90.9%) of the title compound as a almost colorless oil.

**EXAMPLE 198****Preparation of 2-[(6-Methoxy-6-oxohexyl)oxy]-6-[6-[[4-oxo-8-(3-phenylpropyl)-4H-1-benzopyran-7-yl]oxy]hexyl]benzenepropanoic acid methyl ester**

Using the procedure of example 1 with the modification that methanol was used in place of ethanol, 2-[6-[4-acetyl-3-hydroxy-2-(3-phenylpropyl)phenoxy]hexyl]-6-[(6-methoxy-6-oxohexyl)oxy]benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, a pale-yellow oil purified by flash chromatography on silica gel (eluting with 3:1 toluene-ethyl acetate) in 57.4% yield.

**EXAMPLE 199**

**Preparation of 2-[6-[[3,4-Dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl]oxy]hexyl]-6-[(6-methoxy-6-oxohexyl)oxy]benzenepropanoic acid methyl ester**

5

A 1.0 g (1.49 mmol) sample of 2-[(6-methoxy-6-oxohexyl)oxy]-6-[6-[[4-oxo-8-(3-phenylpropyl)-4H-1-benzopyran-7-yl]oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example was catalytically hydrogenated over 10% palladium on carbon in 30 ml of 1:1 methanol-ethyl acetate at room temperature and 1 atmosphere using thin-layer chromatography to monitor the reduction of the starting chromone. The catalyst was filtered and the filtrate was concentrated in vacuo giving an oily product which was purified by flash chromatography. There was obtained 0.38 g (38%) of the title chromanone as a colorless oil.

10

**EXAMPLE 200**

15

**Preparation of 2-[(5-Carboxypentyl)oxy]-6-[6-[[3,4-dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl]oxy]hexyl]benzenepropanoic acid**

The 2-[6-[[3,4-dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl]oxy]hexyl]-6-[(6-methoxy-6-oxohexyl)oxy]benzenepropanoic acid methyl ester from the preceding example (0.38 g; 0.565 mmol) was saponified by stirring with 2 ml of 3N aqueous lithium hydroxide solution, in 15 ml of tetrahydrofuran for 24 hr at room temperature. Work-up as in example 4 followed by flash chromatography on silica gel (eluting with 96:3:1 chloroform-methanol-acetic acid) and recrystallization from hexane-ethyl acetate gave 0.36 g (98%) of the title compound as a colorless solid, mp 97-98°.

20

25

Anal. Calcd. for  $C_{39}H_{48}O_8$ : C, 72.65; H, 7.50. Found: C, 72.49; H, 7.42 %.

**EXAMPLE 201**

**Preparation of rac-(E)-4-[2-(3-Methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]butanoic acid ethyl ester**

30

Using the procedure of example 122, rac-(E)-3-[2-hydroxy-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-2-propenoic acid methyl ester (example 121) was alkylated with ethyl 4-bromobutyrate giving the title compound as a pale-yellow oil in quantitative yield.

35

**EXAMPLE 202**

**Preparation of rac-2-(4-Ethoxy-4-oxobutoxy)-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]-benzenepropanoic acid methyl ester**

40

Using the procedure of example 123, rac-(E)-4-[2-(3-methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]butanoic acid ethyl ester from the preceding example was catalytically hydrogenated giving the title compound as an oil in 90.8% yield.

**EXAMPLE 203**

45

**Preparation of 2-(6-Hydroxyhexyl)-6-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester**

Using the procedure of example 52, rac-2-(4-ethoxy-4-oxobutoxy)-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, a colorless oil, in 72.5% yield.

50

55

**EXAMPLE 204****Preparation of 2-(4-Methoxy-4-oxobutoxy)-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester**

Using the procedure of example 32, 2-(6-hydroxyhexyl)-6-(4-methoxy-4-oxobutoxy)benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, an oil, in quantitative yield.

**EXAMPLE 205****Preparation of 2-(3-Carboxypropoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid**

Using the procedure of example 184, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one was converted into the title compound by alkylation with 2-(4-methoxy-4-oxobutoxy)-6-[6-(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example, followed by saponification in 40% overall yield. The product was a colorless solid, mp 116-117.5 °, recrystallized from acetonitrile.

Anal. Calcd. for  $C_{31}H_{40}O_8$ : C, 68.87; H, 7.46. Found: C, 68.84; H, 7.53 %.

**EXAMPLE 206****Preparation of 2-[(5-Carboxypentyl)oxy]-6-[6-[(5,6,7,8-tetrahydro-5-oxo-1-propyl-2-naphthalenyl)oxy]hexyl]benzenepropanoic acid**

Using the procedure of example 184, 6-hydroxy-5-propyl-1,2,3,4-tetrahydronaphthalen-1-one from example 9 was converted into the title compound by alkylation with 2-[(6-methoxy-6-oxohexyl)oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester from example 156, followed by saponification in 68% overall yield. The diacid product was a colorless solid, mp 100-101 °, recrystallized from hexane-ethyl acetate.

Anal. Calcd. for  $C_{34}H_{46}O_7$ : C, 72.06; H, 8.18. Found: C, 71.95; H, 8.28 %.

**EXAMPLE 207****Preparation of 3-(3-Ethoxy-3-oxopropyl)-4-[[[(trifluoromethyl)sulfonyl]oxy]- $\delta$ -oxobenzenepentanoic acid ethyl ester**

To a solution of 5.80 g (17.2 mmol) of 3-(3-ethoxy-3-oxopropyl)-4-hydroxy- $\delta$ -oxobenzenepentanoic acid ethyl ester from example 140 in 20 ml of pyridine cooled in an ice bath was added trifluoromethanesulfonic anhydride (4 ml, 23.8 mmol) and the mixture was stirred at room temperature for 24.5 hr. The solution was cooled again in an ice bath, a second portion of trifluoromethanesulfonic anhydride (4 ml, 23.8 mmol) was added and the reaction mixture was stirred for an additional 90.5 hr. Water was added and the mixture was worked-up with ether in the usual manner (the combined organic extracts were additionally washed three times with 3N sulfuric acid solution). The crude product was purified by flash chromatography on 900 g of silica gel eluting with hexane-ethyl acetate (6:1) to give 3.28 g (40.6%) of the title compound as a pale-yellow oil.

Anal. Calcd. for  $C_{19}H_{23}F_3O_8S$ : C, 48.72; H, 4.95; F, 12.17; S, 6.85. Found: C, 48.75; H, 4.88; F, 12.06; S, 6.64 %.

**EXAMPLE 208****Preparation of (E/Z)-3-(3-Ethoxy-3-oxopropyl)-4-(6-hydroxyl-1-hexenyl)- $\delta$ -oxobenzenepentanoic acid ethyl ester**

A mixture of 2.23 g (4.76 mmol) of 3-(3-ethoxy-3-oxopropyl)-4-[[[(trifluoromethyl)sulfonyl]oxy]- $\delta$ -oxobenzenepentanoic acid ethyl ester from the preceding example, 2.01 g (5.18 mmol) of (E/Z)-tri-n-butyl-(6-hydroxy-1-hexenyl)stannane, 0.643 g (15.2 mmol) of lithium chloride, 0.363 g (0.31 mmol) of tetrakis(triphenylphosphine)palladium and 3 crystals of 2,6-di-t-butyl-4-methylphenol in 25 ml of dioxane was stirred

at reflux for 3 hr. A second portion of tetrakis(triphenylphosphine)palladium (0.20 g, 0.173 mmol) was added and stirring and refluxing were continued for another 1 hr. Pyridine (3.1 ml) was added followed by 6.2 ml of a solution of 1.2N hydrogen fluoride in pyridine tetrahydrofuran, and the resulting mixture was stirred at room temperature overnight. The mixture was diluted with 300 ml of ether and filtered through Celite. The filtrate was washed once with 75 ml of 10% aqueous hydrochloric acid and work up was completed in the usual manner. The crude product was combined with that obtained from a similar experiment starting from 2.59 g (5.53 mmol) of the triflate and purified by flash chromatography on 750 g of silica gel. Elution with hexane-ethyl acetate (2:1) afforded 3.08 g (71.4%) of the title compound as a pale-yellow oil.

#### 10 **EXAMPLE 209**

##### **Preparation of 4-(6-Bromohexyl)-3-(3-ethoxy-3-oxopropyl)- $\delta$ -oxobenzenepentanoic acid ethyl ester**

To a solution of 0.69 g (1.65 mmol) of (E/Z)-3-(3-ethoxy-3-oxopropyl)-4-(6-hydroxy-1-hexenyl)- $\delta$ -oxobenzenepentanoic acid ethyl ester from the preceding example in 10 ml of ethanol and 10 ml of ethyl acetate was added 0.17 g of 10% palladium on carbon, and the resulting mixture was stirred under 1 atmosphere of hydrogen overnight. The catalyst was filtered with suction on a Celite pad, and the filtrate was concentrated in vacuo to give 0.685 g of an oil. To this crude product was added 1.08 g (3.26 mmol) of carbon tetrabromide, 0.855 g (3.26 mmol) of triphenylphosphine and 25 ml of ether, and the resulting mixture was stirred at room temperature for 23.5 hr. Additional portions of carbon tetrabromide (0.6 g, 1.81 mmol) and triphenylphosphine (0.5 g, 1.91 mmol) were added and the stirring was continued for an additional 26.3 hr. The mixture was diluted with 250 ml of ether and worked-up in the usual manner. The crude product was purified by flash chromatography on 80 g of silica gel eluting with hexane-ethyl acetate (10:1) and afforded 0.496 g (62.2 %) of the title compound as a pale-yellow oil.

Anal. Calcd. for  $C_{24}H_{35}BrO_5$ : C, 59.63; H, 7.30; Br, 16.53. Found: C, 59.20; H, 7.23; Br, 16.82 %.

#### **EXAMPLE 210**

##### **Preparation of 4-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-3-(3-ethoxy)-3-oxopropyl)- $\delta$ -oxobenzenepentanoic acid ethyl ester**

A mixture of 0.43 g (0.89 mmol) of 4-(6-bromohexyl)-3-(3-ethoxy-3-oxopropyl)- $\delta$ -oxobenzenepentanoic acid ethyl ester from the preceding example, 0.188 g (0.91 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one and 0.398 g (2.88 mmol) of anhydrous granular potassium carbonate in 10 ml of 2-butanone was stirred and heated at 89 ° for 19.3 hr. The mixture was filtered with suction and the solid was washed with ether and ethyl acetate. The filtrate was concentrated in vacuo and the crude product was flash-chromatographed on 80 g of silica gel eluting with hexane-ethyl acetate (5:2). There was obtained 0.496 g (91.5 %) of the title compound as a colorless oil.

#### 40 **EXAMPLE 211**

##### **Preparation of 3-(2-Carboxyethyl)-4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]- $\delta$ -oxobenzenepentanoic acid**

To a mixture of 0.442 g (0.73 mmol) of 4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-3-(3-ethoxy-3-oxopropyl)- $\delta$ -oxobenzenepentanoic acid ethyl ester from the preceding example in 7 ml of tetrahydrofuran and 7 ml of water were added 91.7 mg (2.19 mmol) of lithium hydroxide monohydrate and the reaction mixture was stirred at room temperature for 19.3 hr. After being acidified with 16 ml of 3N aqueous sulfuric acid the mixture was worked-up with ethyl acetate in the usual manner. The crude product thus obtained was recrystallized from hexane-ethyl acetate to give 0.309 g (77 %) of the title compound as a white solid, mp 136-139 °.

Anal. Calcd. for  $C_{32}H_{40}O_8$ : C, 69.55; H, 7.30. Found: C, 69.35; H, 7.42 %.

55

**EXAMPLE 212****Preparation of 3-(3-Ethoxy-3-oxopropyl)-4-hydroxybenzenepentanoic acid ethyl ester**

To a solution of 3.91 g (11.6 mmol) of 3-(3-ethoxy-3-oxopropyl)-4-hydroxy- $\delta$ -oxobenzenepentanoic acid ethyl ester (from example 140) in 50 ml of acetic acid was added 0.5 g of 10% palladium on carbon, and the resulting mixture was shaken at room temperature and 310 k Pa in a Parr shaker for 18.5 hr. The mixture was filtered with suction through a Celite pad and the solids washed with ethyl acetate. The filtrate and washes were combined and concentrated in vacuo. The residue was dissolved in 200 ml of ethanol and treated with 5 ml of concentrated sulfuric acid. The resulting mixture was refluxed for 4 hr and then stirred at room temperature overnight. Most of ethanol was removed in vacuo and the residue was worked-up with ether in the usual manner (the combined ether extracts were additionally washed with saturated aqueous sodium bicarbonate solution). The crude product was purified by flash chromatography on 350 g of silica gel eluting with hexane-ethyl acetate (4:1) to give 2.13 g (56.7%) of the title compound as a colorless oil.

Anal. Calcd. for  $C_{18}H_{26}O_5$ : C, 67.06; H, 8.13. Found: C, 66.94; H, 8.20 %.

**EXAMPLE 213****Preparation of 4-(5-Bromopentyloxy)-3-(3-ethoxy-3-oxopropyl)benzenepentanoic acid ethyl ester**

A mixture of 0.655 g (2.03 mmol) of 3-(3-ethoxy-3-oxopropyl)-4-hydroxy-benzenepentanoic acid ethyl ester from the preceding example, 2.80 g (12.2 mmol) of 1,5-dibromopentane, 1.12 g (8.12 mmol) of anhydrous granular potassium carbonate and 35 ml of 2-butanone was stirred at 92 ° for 22 hr. After being cooled to room temperature, the mixture was filtered through anhydrous magnesium sulfate and the solids were washed thoroughly with ethyl acetate and ether. The filtrate and washes were combined and concentrated in vacuo and the crude product was purified by flash chromatography on 80 g of silica gel eluting with hexane-ethyl acetate (4:1). There was obtained 0.804 g (83.9%) of the title compound as a colorless oil.

**EXAMPLE 214****Preparation of 4-[[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-3-(3-ethoxy-3-oxopropyl)benzenepentanoic acid ethyl ester**

A mixture of 1.69 g (3.58 mmol) of 4-(5-bromopentyloxy)-3-(3-ethoxy-3-oxopropyl)benzenepentanoic acid ethyl ester from the preceding example, 0.738 g (3.58 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one, 2.07 g (14.98 mmol) of anhydrous potassium carbonate and 37.5 ml of 2-butanone was stirred and refluxed for 18.5 hr. After being cooled to room temperature the mixture was filtered through anhydrous magnesium sulfate and the solids were washed thoroughly with ethyl acetate. The filtrate and washes were combined and concentrated in vacuo and the crude product was purified by flash chromatography on 250 g of silica gel eluting with hexane-ethyl acetate (4:1). There was obtained 1.93 g (90.1%) of the title compound as a colorless oil.

Anal. Calcd. for  $C_{35}H_{48}O_8$ : C, 70.44; H, 8.11. Found: C, 70.16; H, 8.18 %.

**EXAMPLE 215****Preparation of 3-(2-Carboxyethyl)-4-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepentanoic acid**

To a solution of 1.93 g (3.23 mmol) of 4-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-3-(3-ethoxy-3-oxopropyl)benzenepentanoic acid ethyl ester from the preceding example in 30 ml of tetrahydrofuran and 30 ml of water was added 0.407 g (9.71 mmol) of lithium hydroxide monohydrate and the resulting solution was stirred at room temperature for 46 hr. The reaction mixture was acidified with 60 ml of 3N aqueous sulfuric acid and worked-up with ethyl acetate in the usual manner. The crude product was purified by flash chromatography on 500 g of silica gel eluting with hexane-ethyl acetate (1:1) and afforded 1.07 g (61.0%) of the title compound as a white solid, mp 101-104 °.

Anal. Calcd. for  $C_{31}H_{40}O_8$ : C, 68.87; H, 7.46. Found: C, 68.77; H, 7.52 %.

**EXAMPLE 216****Preparation of 3-(3-Ethoxy-3-oxopropyl)-4-(6-hydroxyhexyl)benzenepentanoic acid ethyl ester**

To a solution of 2.31 g (5.51 mmol) of (E/Z)-3-(3-ethoxy-3-oxopropyl)-4-(6-hydroxy-1-hexenyl)-5-oxobenzenepentanoic acid ethyl ester from example 208 in 100 ml of acetic acid was added 0.5 g of 10% palladium on carbon and the resulting mixture was shaken (Parr apparatus) under 345 k Pa of hydrogen, for 89 hr. The catalyst and solvent were removed as described in previous examples and the residue was dissolved in 50 ml of acetic acid, 25 ml of ethyl acetate and 25 ml of ethanol. To this solution was added 1 g of 10% palladium on carbon and the mixture was hydrogenated as before for 44 hr. The mixture was filtered with suction through Celite, the filter cake washed with ethyl acetate and the filtrate and washes combined and concentrated in vacuo. The residue was dissolved in 100 ml of ethanol, 5 ml of concentrated sulfuric acid was added and the resulting solution was stirred at reflux for 20.5 hr. Most of ethanol was removed under reduced pressure and the residue was worked-up with ether in the usual manner (the combined ether extracts were additionally washed with saturated aqueous sodium bicarbonate solution). The residue was dissolved in 50 ml of toluene and 50 ml of tetrahydrofuran, 1.25 g of 5% rhodium on alumina was added and the resulting mixture was hydrogenated at atmospheric pressure until hydrogen uptake had ceased. The mixture was worked-up as described above and the crude product was purified by flash chromatography on 100 g of silica gel eluting with hexane-ethyl acetate (3:1). There was obtained 0.673 g (30%) of the title compound as a colorless oil.

Anal. Calcd. for  $C_{24}H_{38}O_5$ : C, 70.90; H, 9.42. Found: C, 70.88; H, 9.25 %.

**EXAMPLE 217****Preparation of 4-(6-Bromohexyl)-3-(3-ethoxy-3-oxopropyl)benzenepentanoic acid ethyl ester**

A mixture of 0.673 g (1.65 mmol) of 3-(3-ethoxy-3-oxopropyl)-4-(6-hydroxyhexyl)benzenepentanoic acid ethyl ester from the preceding example, 1.1 g (3.3 mmol) of carbon tetrabromide and 0.9 g (3.3 mmol) of triphenylphosphine in 25 ml of ether was stirred at room temperature for 23 hr. The mixture was diluted with 250 ml of ether and the solution worked-up in the usual manner. The crude product was purified by flash chromatography on 80 g of silica gel eluting with hexane-ethyl acetate (10:1). There was obtained 0.588g (75.7%) of the title compound as a colorless oil.

Anal. Calcd. for  $C_{24}H_{37}BrO_4$ : C, 61.40; H, 7.94; Br, 17.02. Found: C, 61.64; H, 8.07; Br, 16.94 %.

**EXAMPLE 218****Preparation of 4-[6-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-3-(3-ethoxy-3-oxopropyl)benzenepentanoic acid ethyl ester**

Starting with 0.505 g (1.08 mmol) of 4-(6-bromohexyl)-3-(3-ethoxy-3-oxopropyl)benzenepentanoic acid ethyl ester from the preceding example and 0.226 g (1.09 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one, the title compound (0.636 g; 99.3%) was obtained as a colorless oil using the procedure of example 214.

Anal. Calcd. for  $C_{36}H_{50}O_7$ : C, 72.70; H, 8.47. Found: C, 72.57; H, 8.39 %.

**EXAMPLE 219****Preparation of 3-(2-Carboxyethyl)-4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepentanoic acid**

Starting with 0.574 g (0.96 mmol) of 4-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-3-(3-ethoxy-3-oxopropyl)benzenepentanoic acid ethyl ester from the preceding example, the title compound (0.328 g; 63.2%) was obtained as a white solid, mp 107.5-109 °, using the saponification procedure of example 215.

Anal. Calcd. for  $C_{32}H_{42}O_7$ : C, 71.35; H, 7.86. Found: C, 71.33; H, 7.94 %.

**EXAMPLE 220****Preparation of 1,2-Dihydro-9-methoxy-3H-naphtho[2,1-b]pyran-3-one**

A solution of 2.64 g (15.2 mmol) of 7-methoxy-2-naphthalenol, 5.27 g (30.2 mmol) of triethyl orthoacrylate, and 0.77 g (7.6 mmol) of trimethylacetic acid in 30 ml of toluene was stirred and refluxed for 22.5 hr. A second run was carried out starting with 2.09 g (12 mmol) of 7-methoxy-2-naphthalenol, 4.17 g (23.9 mmol) of triethyl orthoacrylate and 0.61 g (6 mmol) of trimethylacetic acid in 15 ml of toluene refluxing for 18.7 hr. After being cooled to room temperature, the solutions from these two runs were combined and diluted with 50 ml of ether. The resulting solution was washed with 5% sodium hydroxide solution and work-up was completed in the usual manner to give 10.98 g of a crude product. To this material was added 100 ml of ether and 100 ml of 10% aqueous hydrochloric acid, and the mixture was stirred at room temperature for 2 hr. Work-up with ether in the usual manner gave 9.51 g of an oily residue. This product was dissolved in 200 ml of toluene, 1.0 g (5.26 mmol) of p-toluenesulfonic acid monohydrate was added, and the resulting solution was stirred and refluxed with removal of water using a Dean-Stark trap for 21.5 hr. After being cooled to room temperature the solution was washed with 100 ml of saturated sodium bicarbonate solution and worked-up as usual. The crude product (7.97 g) was purified on 500 g of silica gel eluting with hexane-chloroform (2:1 and 1:1) to give 5.38 g (86.8%) of the title compound as a white solid, mp 100-101 °.

Anal. Calcd. for  $C_{14}H_{12}O_3$ : C, 73.67; H, 5.30. Found: C, 73.59; H, 5.33 %.

**EXAMPLE 221****Preparation of 1,2-Dihydro-9-hydroxy-3H-naphtho[2,1-b]pyran-3-one**

A mixture of 2.57 g (11.3 mmol) of 1,2-dihydro-9-methoxy-3H-naphtho[2,1-b]pyran-3-one from the preceding example and 7.86 g (68.0 mol) of pyridine hydrochloride was heated at 200-230 ° for 2.5 hr. After being cooled to room temperature the reaction mixture was treated with 100 ml of water and worked-up with ethyl acetate in the usual manner. The crude product (2.52 g) was dissolved in 150 ml of toluene, treated with 0.31 g (1.63 mmol) of p-toluenesulfonic acid monohydrate, and the resulting solution was stirred at reflux for 3.5 hr with removal of water using a Dean-Stark trap. The solution was diluted with 300 ml of ethyl acetate, washed three times with saturated sodium bicarbonate solution, and work-up was completed in the usual manner. The crude product was purified by flash chromatography on 300 g of silica gel eluting with hexane-ethyl acetate (3:1) to give 2.06 g (85.3%) of the title compound as a light-brown solid, mp 194-202 ° (recrystallized from ethyl acetate).

Anal. Calcd. for  $C_{13}H_{10}O_3$ ; C, 72.89; H, 4.71. Found: C, 72.69; H, 4.73 %.

**EXAMPLE 222****Preparation of [(2,3-Dihydro-3-oxo-1H-naphtho[2,1-b]pyran-9-yl)oxy]acetic acid 1,1-dimethylethyl ester**

A mixture of 2.73 g (12.7 mmol) of 1,2-dihydro-9-hydroxy-3H-naphtho[2,1-b]pyran-3-one from the preceding example, 6.2 g (31.8 mmol) of t-butyl bromoacetate, 7.04 g (51.0 mmol) of anhydrous granular potassium carbonate and 70 ml of 2-butanone was stirred at 60 ° for 17 hr. After being cooled to room temperature the mixture was filtered and the solids washed thoroughly with ether and ethyl acetate. The filtrate and washes were combined and concentrated in vacuo. The crude product was purified by flash chromatography on 200 g of silica gel eluting with hexane-ethyl acetate (4:1) to give 1.23 g of 2,7-bis[2-(1,1-dimethylethoxy)-2-oxoethoxy]-1-naphthalenepropanoic acid 2-(1,1-dimethylethoxy)-2-oxoethyl ester. Further elution then afforded 2.97 g (71.0%) of the title compound as a pale-yellow solid, mp 117.5-118.5 ° (recrystallized from hexane-ethyl acetate).

Anal. Calcd. for  $C_{19}H_{20}O_5$ : C, 69.50; H, 6.14. Found: C, 69.50; H, 6.02 %.

**EXAMPLE 223****Preparation of 7-(2-Ethoxy-2-oxoethoxy)-2-hydroxy-1-naphthalenepropanoic acid ethyl ester**

To a solution of 2.97 g (9.0 mmol) of [(2,3-dihydro-3-oxo-1H-naphtho[2,1-b]pyran-9-yl)oxy]acetic acid 1,1-dimethylethyl ester from the preceding example in 120 ml of ethanol was added 2 ml of concentrated



sulfuric acid and the resulting solution was allowed to stir at room temperature for 13 days. Most of ethanol was removed under reduced pressure and the residue was dissolved in ether. The solution was washed with saturated aqueous sodium bicarbonate solution and work-up was completed in the usual manner. The crude product was purified by flash chromatography on 150 g silica gel eluting with hexane ethyl acetate (4:1). There was obtained 2.69 g (86.0%) of the title compound as a white solid, mp 112-113 °.

Anal. Calcd. for  $C_{19}H_{22}O_6$ : C, 65.88; H, 6.40. Found: C, 65.72; H, 6.36 %.

#### EXAMPLE 224

##### Preparation of 2-[(5-Bromopentyl)oxy]-7-(2-ethoxy-2-oxoethoxy)-1-naphthalenepropanoic acid ethyl ester

A mixture of 1.08 g (3.12 mmol) of 7-(2-ethoxy-2-oxoethoxy)-2-hydroxy-1-naphthalenepropanoic acid ethyl ester from the preceding example, 4.31 g (18.7 mmol) of 1,5-dibromopentane, 2.59 g (18.7 mmol) of anhydrous granular potassium carbonate and 70 ml of 2-butanone was heated at 65 ° for 24 hr. After being cooled to room temperature, the mixture was filtered through anhydrous magnesium sulfate. The solids were washed thoroughly with ethyl acetate and the filtrate and washes were combined and concentrated in vacuo. To the residue was added 60 ml of ethanol and 1 ml of concentrated sulfuric acid and the resulting solution was stirred at room temperature for 17.5 hr. Most of the ethanol was removed under reduced pressure and the residue was flash-chromatographed on 110 g of silica gel eluting with hexane-ethyl acetate (6:1) to give 1.15 g (74.4%) of the title compound as an off-white, waxy solid, mp 29.5-32 °.

Anal. Calcd. for  $C_{24}H_{31}BrO_6$ : C, 58.19; H, 6.31; Br, 16.13. Found: C, 57.92; H, 6.28; Br, 16.22 %.

#### EXAMPLE 225

##### Preparation of 2-[[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-7-(2-ethoxy-2-oxoethoxy)-1-naphthalenepropanoic acid ethyl ester

A mixture of 0.454 g (2.2 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one, 1.09 g (2.2 mmol) of 2-[(5-bromopentyl)oxy]-7-(2-ethoxy-2-oxoethoxy)-1-naphthalenepropanoic acid ethyl ester from the preceding example, 1.23 g (8.9 mmol) of anhydrous granular potassium carbonate and 32.5 ml of 2-butanone was heated at 94 ° for 22 hr. After being cooled to room temperature, the mixture was filtered through some anhydrous magnesium sulfate. The solids were washed thoroughly with ethyl acetate and the filtrate and washes were combined and concentrated in vacuo. The residue was flash-chromatographed on 200 g of silica gel eluting with hexane-ethyl acetate (2:1) and afforded 1.11 g (81%) of the title compound as a white solid, mp 68-69.5 °.

Anal. Calcd. for  $C_{36}H_{44}O_9$ : C, 69.66; H, 7.14. Found: C, 69.74; H, 7.44 %.

#### EXAMPLE 226

##### Preparation of 7-(Carboxymethoxy)-2-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-1-naphthalenepropanoic acid

A mixture of 0.86 g (1.39 mmol) of 2-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-7-(2-ethoxy-2-oxoethoxy)-1-naphthalenepropanoic acid ethyl ester from the preceding example, 0.177 g (4.21 mmol) of lithium hydroxide monohydrate, 10.1 ml of tetrahydrofuran, and 10.1 ml of water was stirred at room temperature for 41.5 hr. A second saponification was carried out with 0.188 g (0.3 mmol) of the starting ester, 38 mg (0.9 mmol) of lithium hydroxide monohydrate, 2.2 ml of tetrahydrofuran and 2.2 ml of water. After combining the two reaction mixtures, 30 ml of 3N aqueous sulfuric acid was added, and the mixture was worked-up with ethyl acetate in the usual manner. The crude product was crystallized from hexane-ethyl acetate to give 0.803 g (84.3%) of the title compound as an off-white solid, mp 175-177.5 °.

Anal. Calcd. for  $C_{32}H_{36}O_9$ : C, 68.07; H, 6.43. Found: C, 68.09; H, 6.55 %.

**EXAMPLE 227****Preparation of 1,2-Dihydro-8-methoxy-3H-naphtho[2,1-b]pyran-3-one**

5 Starting with a solution of 6.29 g (36.1 mmol) of 6-methoxy-2-naphthalenol, 12.58 g (72.2 mmol) of triethyl orthoacrylate and 1.84 g (18.1 mmol) of trimethylacetic acid in 70 ml of toluene, the title compound (7.12g; 86.4%) was obtained as a white solid, mp 122-123 °, using the procedure of example 220.

Anal. Calcd. for  $C_{14}H_{12}O_3$ : C, 73.67; H, 5.30. Found: C, 73.41; H, 5.16 %.

**EXAMPLE 228****Preparation of 1,2-Dihydro-8-hydroxy-3H-naphtho[2,1-b]pyran-3-one**

15 Starting with 4.84 g (21.2 mmol) of 1,2-dihydro-8-methoxy-3H-naphtho[2,1-b]pyran-3-one from the preceding example, the title compound (3.19g; 70.3%) was obtained as an off-white solid, mp 189-199 ° (recrystallized from ethanol-ethyl acetate), using the procedure of example 221.

Anal. Calcd. for  $C_{13}H_{10}O_3$ : C, 72.89; H, 4.71. Found: C, 72.81; H, 4.69 %.

**EXAMPLE 229****Preparation of [(2,3-Dihydro-3-oxo-1H-naphtho[2,1-h]pyran-8-yl)oxy]acetic acid 1,1-dimethylethyl ester**

25 A mixture of 2.18 g (10.2 mmol) of 1,2-dihydro-8-hydroxy-3H-naphtho[2,1-b]pyran-3-one from the preceding example, 4.84 g (24.8 mmol) of t-butyl bromoacetate, 5.63 g (40.7 mmol) of anhydrous granular potassium carbonate and 55.5 ml of 2-butanone was heated at 60 ° for 24 hr. A second portion of t-butyl bromoacetate (0.5 ml, 3.1 mmol) was added and the reaction was allowed to proceed for another 17 hr. After being cooled to room temperature, the mixture was filtered and the solids were washed with ethyl acetate and ether. The filtrate and washes were combined and concentrated in vacuo and the crude product 30 was flash-chromatographed on 360 g of silica gel eluting with hexane-ethyl acetate (7:1 then 6:1) and afforded 3.04 g (91.0%) of the title compound as a white solid, mp 95-96 °.

Anal. Calcd. for  $C_{19}H_{20}O_5$ : C, 69.50; H, 6.14. Found: C, 69.66; H, 6.23 %.

**EXAMPLE 230****Preparation of 2-[[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-6-(2-ethoxy-2-oxoethoxy)-1-naphthalenepropanoic acid ethyl ester**

40 Starting with [(2,3-dihydro-3-oxo-1H-naphtho[2,1-b]pyran-8-yl)oxy]acetic acid 1,1-dimethylethyl ester from the preceding example, the title compound was obtained as a white solid, mp 100-102.5 °, using the procedures of examples 223-225.

Anal. Calcd. for  $C_{36}H_{44}O_9$ : C, 69.66; H, 7.15. Found: C, 69.65; H, 7.12 %.

**EXAMPLE 231****Preparation of 6-(Carboxymethoxy)-2-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-1-naphthalenepropanoic acid**

50 Starting with 0.736 g (1.19 mmol) of 2-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-6-(2-ethoxy-2-oxoethoxy)-1-naphthalenepropanoic acid ethyl ester from the preceding example, the title compound (0.352 g; 52.6%) was obtained as a white solid, mp 160.5-163 ° (recrystallized from hexane-ethyl acetate), using the procedure of example 226.

Anal. Calcd. for  $C_{32}H_{36}O_9$ : C, 68.07; H, 6.43. Found: C, 68.03; H, 6.55 %.

**EXAMPLE 232****Preparation of 2-(Bromomethyl)-6-methoxyquinoline**

5 A solution of 10 g (57.7 mmol) of 6-methoxy-2-methylquinoline and 30 drops of pyridine in 40 ml of N,N-dimethylformamide was stirred at 60 ° while a solution of 16.21 g (57.7 mmol) of tribromoacetaldehyde in 20 ml of N,N-dimethylformamide was added over 15 min. The reaction mixture was stirred for another 2 hr and then cooled and poured onto 600 ml of ice-water. Work-up with ethyl acetate was carried out in the usual manner. The crude product was purified by flash chromatography on 800 g of silica gel eluting with  
 10 hexane-ethyl acetate (4:1) and afforded 4.45 g (30.6%) of the title compound as a violet solid. An analytical sample was obtained by recrystallization from ethanol to give colorless crystals, mp 103 °.

Anal. Calcd. for C<sub>11</sub>H<sub>10</sub>BrNO: C, 52.41; H, 4.00; Br, 31.70; N, 5.56. Found: C, 52.53; H, 3.85; Br, 31.71; N, 5.50 %.

**EXAMPLE 233****Preparation of 6-Methoxy-2-quinolinepropanoic acid 1,1-dimethylethyl ester**

To a solution of diisopropylamine (7.4 ml, 52.8 mmol) in 70 ml of tetrahydrofuran cooled to -78 ° was  
 20 added a solution of 1.6M n-butyllithium in hexane (31.4 ml, 50.2 mmol). After being stirred for 12 minutes, the resulting solution of lithium diisopropylamide was treated with a solution of t-butyl acetate (4.81 g, 41.4 mmol) in 70 ml of tetrahydrofuran, added slowly through an addition funnel. The reaction mixture was allowed to warm gradually to 10 ° over 3.75 hr and then recooled to -78 ° whereupon a solution of 2-(bromomethyl)-6-methoxyquinoline from the preceding example (3.46 g, 13.7 mmol) in 40 ml of  
 25 tetrahydrofuran was added and the reaction was allowed to stir overnight at room temperature. The resulting solution was worked-up with ether in the usual manner. Flash chromatography of the crude product on 360 g of silica gel eluting with hexane-ethyl acetate (4:1) afforded 1.31 g (33.8%) of the title compound as an orange oil.

Anal. Calcd. for C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.90; H, 7.34; N, 4.75 %.

30

**EXAMPLE 234****Preparation of 6-Hydroxy-2-quinolinepropanoic acid ethyl ester**

35 A mixture of 1.25 g (4.42 mmol) of 6-methoxy-2-quinolinepropanoic acid 1,1-dimethylethyl ester from the preceding example and 10 ml of 48% hydrobromic acid solution was heated at reflux for 23 hr then poured onto crushed ice. Concentrated ammonium hydroxide solution was added slowly until the solution became neutral at which point it was concentrated to dryness under reduced pressure. To the residue were added 500 ml of ethanol followed by 20 ml of acetyl chloride and the resulting mixture was stirred at reflux  
 40 for 17 hr. Most of ethanol was removed under reduced pressure, 150 ml of saturated aqueous sodium bicarbonate and 60 ml of water were added and the mixture was worked-up with ethyl acetate in the usual manner. The crude product was flash-chromatographed on 110 g of silica gel eluting with hexane-ethyl acetate (3:1) to give 0.819 g (75.5%) of the title compound as a white solid, mp 126.5-127.5 °.

Anal. Calcd. for C<sub>14</sub>H<sub>15</sub>NO<sub>3</sub>: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.54; H, 5.99; N, 5.55 %.

45

**EXAMPLE 235****Preparation of 6-Hydroxy-2,5-quinolinedipropanoic acid diethyl ester**

50 A solution of 0.779 g (3.17 mmol) of 6-hydroxy-2-quinolinepropanoic acid ethyl ester from the preceding example, 1.11 g (6.38 mmol) of triethyl orthoacrylate and 0.491 g (4.81 mmol) of trimethylacetic acid in 21 ml of toluene was stirred at reflux for 16 hr. A solution of 0.283 g (1.62 mmol) of triethyl orthoacrylate in 3 ml of toluene was added and the reaction was allowed to stir under reflux for another 23 hr. After being cooled to room temperature, the solution was diluted with ether, washed three times with saturated aqueous sodium bicarbonate and work-up was completed in the usual manner. To the residue was added 25 ml of  
 55 ether, 25 ml of water and 1.21 g (6.36 mmol) of p-toluenesulfonic acid monohydrate and the resulting mixture was stirred at room temperature for 1.5 hr. Saturated aqueous sodium bicarbonate was added and the mixture was worked-up with ethyl acetate in the usual manner. The crude product was flash-

chromatographed on 110 g of silica gel eluting with hexane-ethyl acetate (3:1 and 2:1) and afforded 0.909 g (82.9%) of the title compound as a white solid, mp 74-76 °.

Anal. Calcd. for  $C_{19}H_{23}NO_5$ : C, 66.07; H, 6.71; N, 4.06. Found: C, 66.28; H, 6.88; N, 3.93 %.

#### 5 **EXAMPLE 236**

##### **Preparation of 6-[(5-Bromopentyl)oxy]-2,5-quinolinedipropanoic acid diethyl ester**

A mixture of 0.866 g (2.51 mmol) of 6-hydroxy-2,5-quinolinedipropanoic acid ethyl ester from the preceding example, 2.33 g (10.1 mmol) of 1,5-dibromopentane, 1.75 g (12.7 mmol) of anhydrous granular potassium carbonate and 25 ml of 2-butanone was stirred at 90 ° for 8.25 hr and at room temperature for another 37 hr. The mixture was filtered through anhydrous magnesium sulfate and the solids were washed with ethyl acetate. The filtrate and washes were combined and concentrated under reduced pressure. The residue was dissolved in 200 ml of ethanol, 1.21 g (6.36 mmol) of p-toluenesulfonic acid monohydrate was added and the resulting solution was stirred at room temperature for 22 hr. Most of the ethanol was removed under reduced pressure. The residue was treated with saturated aqueous sodium bicarbonate solution and worked-up with ethyl acetate in the usual manner. The crude product was partially purified by flash chromatography on 110 g of silica gel eluting with hexane-ethyl acetate (3:1 and 2:1) and gave 1.03 g of the title compound.

#### 20 **EXAMPLE 237**

##### **Preparation of 6-[[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-2,5-quinolinedipropanoic acid diethyl ester**

A mixture of 0.96 g of the partially purified 6-[(5-bromopentyl)oxy]-2,5-quinolinedipropanoic acid diethyl ester from the preceding example, 0.402 g (1.95 mmol) of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one, 1.08 g (7.8 mmol) of anhydrous granular potassium carbonate and 25 ml of 2-butanone was stirred at 90 ° for 18 hr. A second portion of 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one (0.117 g, 0.57 mmol) was added and the reaction was continued for another 22.5 hr. The mixture was cooled and filtered through anhydrous magnesium sulfate and the solids were washed with ethyl acetate. The filtrate and washes were combined and concentrated under reduced pressure. The crude product was purified by flash chromatography on 110 g of silica gel eluting with hexane-ethyl acetate (5:2) to give 0.66 g (54.8%) of the title compound as a white solid, mp 59-61 °.

Anal. Calcd. for  $C_{35}H_{45}NO_8$ : C, 69.77; H, 7.32; N, 2.26. Found: C, 69.78; H, 7.09; N, 2.39 %.

#### **EXAMPLE 238**

##### **Preparation of 6-[[5-[(3,4-Dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-2,5-quinolinedipropanoic acid**

To a mixture of 0.126 g (0.2 mmol) of 6-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-2,5-quinolinedipropanoic acid diethyl ester from the preceding example, 2.5 ml of tetrahydrofuran and 2.5 ml of water were added 25.7 mg (0.61 mmol) of lithium hydroxide monohydrate. The mixture was stirred at room temperature for 28.5 hr, acidified with 7 drops of 3N aqueous sulfuric acid and worked-up with ethyl acetate in the usual manner. The residue was taken up in small amount of ethyl acetate and methanol and filtered. Most of the solvent in the filtrate was evaporated and hexane was then added to induce crystallization. The title compound (33.4 mg, 29.1%) was thus obtained as a white solid, mp 123-128 °.

#### **EXAMPLE 239**

##### **Preparation of rac-(E)-7-[2-(3-Methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]heptanoic acid ethyl ester**

Using the procedure of example 122, rac-(E)-3[2-hydroxy-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenyl]-2-propenoic acid methyl ester (example 121) was alkylated with ethyl 7-bromoheptanoate giving the title compound as a pale-yellow oil in 98% yield.

**EXAMPLE 240**

Preparation of rac-2-[(7-Ethoxy-7-oxoheptyl)oxy]-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]-benzenepropanoic acid methyl ester

Using the procedure of example 123, rac-(E)-7-[2-(3-methoxy-3-oxo-1-propenyl)-3-[6-[(tetrahydro-2H-pyran-2-yl)oxy]-1-hexynyl]phenoxy]heptanoic acid ethyl ester from the preceding example was catalytically hydrogenated giving the title compound as an oil in quantitative yield.

**EXAMPLE 241**

Preparation of 2-(6-Hydroxyhexyl)-6-[(7-methoxy-7-oxoheptyl)oxy]benzenepropanoic acid methyl ester

Using the procedure of example 52, rac-2-[(7-ethoxy-7-oxoheptyl)oxy]-6-[6-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, a colorless oil, in 76% yield.

**EXAMPLE 242**

Preparation of 2-[(7-Methoxy-7-oxoheptyl)oxy]-6-[6-[(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester

Using the procedure of example 32, 2-(6-hydroxyhexyl)-6-[(7-methoxy-7-oxoheptyl)oxy]-benzenepropanoic acid methyl ester from the preceding example was converted into the title compound, an oil, in quantitative yield.

**EXAMPLE 243**

Preparation of 2-[(6-Carboxyhexyl)oxy]-6-[6-(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]-hexyl]benzenepropanoic acid

Using the procedure of example 184, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one was converted into the title compound by alkylation with 2-[(7-methoxy-7-oxoheptyl)oxy]-6-[6-(methylsulfonyl)oxy]hexyl]benzenepropanoic acid methyl ester from the preceding example, followed by saponification in 55% overall yield. The product was a colorless solid, mp 91-93 °, recrystallized from hexane-ethyl acetate.

Anal. Calcd. for C<sub>34</sub>H<sub>46</sub>O<sub>8</sub>: C, 70.08, H, 7.96. Found: C, 70.10; H, 7.99%.

**EXAMPLE 244**

Preparation of 2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid disodium salt

The dicarboxylic acid from example 157 (10 mmol) was neutralized with 20 ml (20 mmol) of 1N aqueous sodium hydroxide solution. The resulting mixture was diluted with more water and the solution was freeze-dried giving the title salt.

**EXAMPLE 245**

TABLET FORMULATION (Wet Granulation)					
Ingredients		mg/tablet			
1.	Compound A.*	0.1	0.5	5.0	5.0
2.	Lactose Anhydrous DTG	106.9	106.5	102.0	118.0
3.	Avicel PH 102	15.0	15.0	15.0	25.0
4.	Modified Starch	7.0	7.0	7.0	10.0
5.	Magnesium Stearate	1.0	1.0	1.0	2.0
<b>TOTAL</b>		<b>130.0</b>	<b>130.0</b>	<b>130.0</b>	<b>160.0</b>

\* Compound A is

2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy-  
]hexyl]benzenepropanoic acid

**Manufacturing Procedure:**

- 1) Dissolve Item 1 in a suitable solvent such as alcohol.
- 2) Spread the solution in Step 1 over Item 2, dry.
- 3) Add Items 3 and 4 and mix for 10 minutes.
- 4) Add magnesium stearate and mix for 3 minutes and compress.

**EXAMPLE 246**

CAPSULE FORMULATION					
Ingredients		mg/capsule			
1.	Compound A	0.1	0.5	5.0	25.0
2.	Lactose Hydrous	168.9	168.5	159.0	123.0
3.	Corn Starch	20.0	20.0	25.0	35.0
4.	Talc	10.0	10.0	10.0	15.0
5.	Magnesium Stearate	1.0	1.0	1.0	2.0
<b>TOTAL</b>		<b>200.0</b>	<b>200.0</b>	<b>200.0</b>	<b>200.0</b>

**Manufacturing Procedure:**

- 1) Mix Items 1, 2 and 3 in a suitable mixer for 30 minutes.
- 2) Add Items 4 and 5 and mix for 3 minutes.
- 3) Fill into suitable capsule.

**EXAMPLE 247**

5

10

TABLET FORMULATION (Wet Granulation)			
Item	Ingredient	mg/ tablet	
1.	Compound A	100	500
2.	Lactose	30	150
3.	Pregelatinized Starch	6	30
4.	Microcrystalline Cellulose	30	150
5.	Magnesium Stearate	1	6
TOTAL		167	836

15

**Manufacturing Procedure:**

20

- 1) Mix Items 1, 2, 3 and 4 and granulate with water.
- 2) Dry the granulation at 50° .
- 3) Pass the granulation through suitable milling equipment.
- 4) Add Item 5 and mix for three minutes; compress on a suitable press.

**EXAMPLE 248**

25

30

35

CAPSULE FORMULATION			
Item	Ingredient	mg/ capsule	
1.	Compound A	100	500
2.	Corn Starch (Pregelatinized)	8	40
3.	Modified Starch	4	20
4.	Talc	4	20
5.	Magnesium Stearate	1	2
TOTAL		117	582

**Manufacturing Procedure:**

40

- 1) Mix Items 1, 2, and 3 and wet granulate with water. Dry at 45° overnight.
- 2) Mill through suitable screen using appropriate milling equipment.
- 3) Add Items 4 and 5 and mix for five minutes.
- 4) Fill into suitable capsule.

45

**EXAMPLE 249**

50

55

INHALATION AEROSOL FORMULATION (Suspension)		
Item	Ingredients	% w/w
1.	Compound A	1.0
2.	Sorbitan Trioleate	0.5
3.	Freon 12	64.0
4.	Freon 11	18.5
5.	Freon 114	16.0
TOTAL		100%

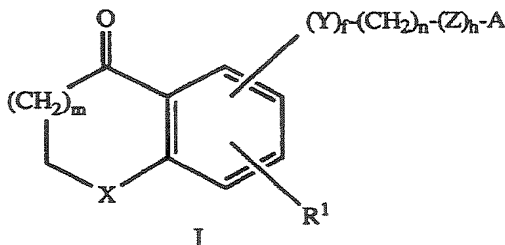
**Manufacturing Procedure:**

- 1) Mix Items 1 and 2 into 4 and homogenize.
- 2) Fill the concentrate suspension from Step 1 into a suitable can and place in valve and crimp to seal container.
- 3) Pressure-fill a 80:20 mixture of Items 3 and 5.

**NOTE:** A suitable valve may be used to deliver 25 to 100 microliters in volume.

**Claims**

1. A compound of the general formula



wherein

X is -O- or -CH₂-;

Y is -O-, -CH₂-CH₂-, -CH=CH-, -C≡C- or -OCH₂C₆H₄-;

Z is -CH₂-CH₂-, -CH=CH- or -C≡C-;

R¹ is hydrogen, lower alkyl, lower alkenyl, cycloalkyl or aralkyl;

A is -B or -O-B;

B is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group -COR², -(O)ₜ-(W)ₛ-COR² or -(CH=CH)ₚCOR² and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)ₖ-(W)ₛ'-E or -(Q)ₖ-(W)ₛ''-

C₆H₄-(W)ₛ''-E, provided that no more than one of said substituents is -(Q)ₖ-(W)ₛ'-E or -(Q)ₖ-(W)ₛ''-

C₆H₄-(W)ₛ''-E;

E is -COR² or R²;

W is -CR³R⁴-;

Q is -O- or carbonyl;

R² is hydroxy, lower alkoxy or -NR³R⁴;

R³ and R⁴, each occurrence, independently, are hydrogen or lower alkyl;

f, h, k, m and t, independently, are 0 or 1;

n, s and s', independently, are an integer from 1 to 12;

p is an integer from 1 to 2;

s'' and s''', independently, are a integer from 0 to 12; and

C₆H₄ is a 1,2-, 1,3- or 1,4-phenylene moiety,

their geometric and optical isomers and, when R² is hydroxy, pharmaceutically acceptable salts thereof with bases.

2. A compound according to Claim 1, wherein E is -COR².

3. A compound according to Claim 1 or 2, wherein Y is -O-, R¹ is lower alkyl, n is 3-8 and m and f are 1.

4. A compound according to Claim 3, wherein Y is -O-, R¹ is lower alkyl, h is 0, m and f are 1, n is 3-8 and A is -O-B, and B is a mono-, di- or tricyclic aromatic moiety.

5. A compound according to Claim 1 or 2, wherein Y is -O-, R¹ is lower alkyl or aralkyl, h is 0, m and f are 1, n is 3-8 and A is -B, wherein B is a monocyclic aromatic moiety, preferably phenyl, substituted by -(O)ₜ-(W)ₛ-COR² and -(Q)ₖ-(W)ₛ'-E, wherein E is -COR², Q is -O-, R² is hydroxy, t is 0, s is 2, k is 1



and s' is 1 to 12.

6. A compound according to Claim 5, wherein X and Y are -O-, R<sup>1</sup> is lower alkyl, h is 0, m and f are 1, n is 3-8 and A is -B, wherein B is a monocyclic aromatic moiety, preferably phenyl, substituted by -(O), -(W)<sub>s</sub> -COR<sup>2</sup> and -(Q)<sub>k</sub>-(W)<sub>s</sub> -E, wherein E is -COR<sup>2</sup>, Q is -O-, R<sub>2</sub> is hydroxy, t is 0, s is 2, k is 1 and s' is 1 to 6.
7. 2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid.
8. 2-(4-Carboxybutoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid.
9. 5-(3-Carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid.
10. 6-(4-Carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid.
11. 2-[(5-Carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid.
12. (E)-3-[5-(3-Carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]phenyl]-2-propenoic acid.
13. 2-[(4-Carboxy-4-methylpentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid;  
 3-(2-carboxyethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepentanoic acid;  
 2-(2-carboxyethyl)-3-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenehexanoic acid;  
 2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-6-[(5-hydroxypentyl)oxy]-benzenepropanoic acid;  
 2-[(5-carboxypentyl)oxy]-6-[6-[(5,6,7,8-tetrahydro-5-oxo-1-propyl-2-naphthalenyl)oxy]hexyl]-benzenepropanoic acid;  
 5-[(3-carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid;  
 5-[(3-carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]-benzenepropanoic acid;  
 5-[(3-carboxyphenyl)carbonyl]-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyloxy]-benzenepropanoic acid;  
 5-(3-carboxypropoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid;  
 5-(4-carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid hemihydrate;  
 5-[(3-carboxyphenyl)carbonyl]-2-[7-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]heptyloxy]-benzenepropanoic acid;  
 5-[(3-carboxyphenyl)carbonyl]-2-[8-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]octyloxy]-benzenepropanoic acid;  
 5-[(4-carboxyphenyl)carbonyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-benzenepropanoic acid;  
 3-(2-carboxymethyl)-4-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-γ-oxobenzenebutanoic acid;  
 5-[2-(2-carboxyphenyl)-1-oxoethyl]-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid;  
 6-(carboxymethoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]-1-naphthalenepropanoic acid;  
 2-[[5-[(3,4-dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl)oxy]pentyloxy]oxy]benzenepropanoic acid.

acid; or

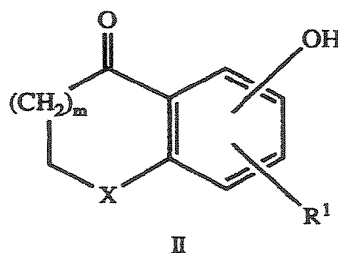
2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid.

14. Compounds in accordance with any one of claims 1-13 for use as therapeutically active substances.

15. Compounds in accordance with any one of claims 1-13 for use in the control or prevention of inflammatory diseases, such as psoriasis, inflammatory bowel disease, asthma, allergy, arthritis, dermatitis, gout, pulmonary disease, ischemia/reperfusion injury, and trauma induced inflammation, such as spinal cord injury.

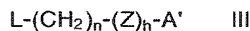
16. A process for the manufacture of a compound in accordance with any one of claims 1-13, which comprises

(a) for the manufacture of compounds of formula I wherein Y is -O-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy and the remaining symbols are as previously described, reacting a compound of the general formula



wherein X, R<sup>1</sup> and m are as previously described,

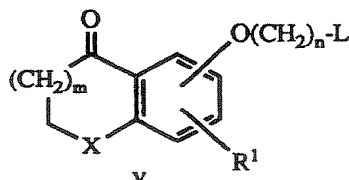
with a compound of the general formula



wherein Z, h and n are as previously described, A' is -B' or -O-B', wherein B' is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group -COR<sup>2'</sup>, -(O)<sub>t</sub>(W)<sub>s</sub>COR<sup>2'</sup> or -(CH=CH)<sub>p</sub>COR<sup>2'</sup> and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)<sub>k</sub>-(W)<sub>s</sub>-E' or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E', provided that no more than one of said substituents is -(Q)<sub>k</sub>-(W)<sub>s</sub>-E' or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E', wherein E' is -COR<sup>2'</sup> or R<sup>2'</sup> and R<sup>2'</sup> is lower alkoxy and Q, W, C<sub>6</sub>H<sub>4</sub>, k, p, s, s', s'', s''' and t are as previously described, and L is a leaving group,

or

(b) for the manufacture of compounds of formula I wherein Y is -O-, f is 1, A is -O-B and R<sup>2</sup> in symbol A is lower alkoxy and the remaining symbols are as previously described, reacting a compound of the general formula



wherein X, R<sup>1</sup>, L, m and n are as previously described,

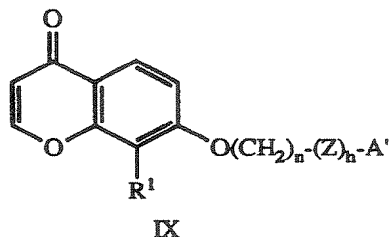
with a compound of the general formula

HO-B'

wherein B' is as previously described,

or

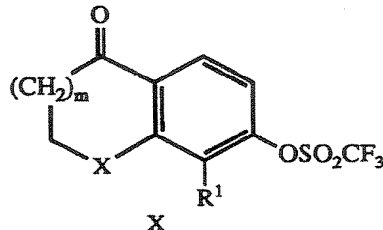
(c) for the manufacture of compounds of formula I wherein X and Y, independently, are -O-, f and m, independently, are 1 and R<sup>2</sup> in symbol A is lower alkoxy, with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, catalytically hydrogenating a compound of the general formula



wherein Z, R<sup>1</sup>, A', h and n are as previously described,

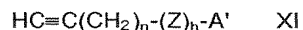
or

(d) for the manufacture of compounds of formula I wherein Y is -C≡C-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy, with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, reacting a compound of the general formula



wherein X, R<sup>1</sup> and m are as previously described,

with a compound of the general formula



wherein Z, A', h and n are as previously described,

or

(e) for the manufacture of compounds of formula I wherein Y is -CH₂CH₂-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy, with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, catalytically hydrogenating a compound of formula I wherein Y is -C≡C-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy, with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described,

or

(f) for the manufacture of compounds of formula I wherein Y is -O-, f is 1 and R<sup>2</sup> in symbol A is hydroxy, and the remaining symbols are as previously described, saponifying a compound of

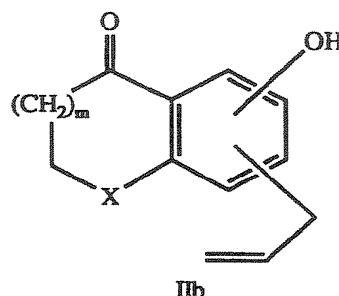
formula I wherein Y is -O-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy, and the remaining symbols are as previously described,

or

(g) for the manufacture of compounds of formula I wherein Y is -C≡C- or -CH<sub>2</sub>CH<sub>2</sub>-, f is 1 and R<sup>2</sup> in symbol A is hydroxy with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, saponifying a compound of formula I wherein Y is -C≡C- or -CH<sub>2</sub>CH<sub>2</sub>-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy, with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described,

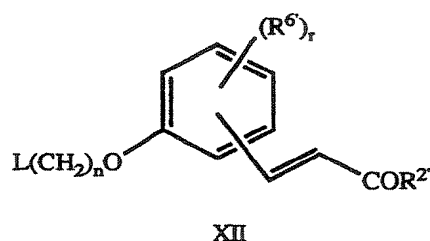
or

(h) for the manufacture of compounds of formula I wherein Y is -O-, f is 1, h is zero, R<sup>1</sup> is allyl, A is -O-B and B is phenyl substituted by the group -CH=CH-COR<sup>2</sup> and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)<sub>k</sub>-(W)<sub>s</sub>-E or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s'</sub>-E, provided that no more than one of said substituents is -(Q)<sub>k</sub>-(W)<sub>s</sub>-E or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s'</sub>-E, with -COR<sup>2</sup> being lower alkoxy carbonyl, and the remaining symbols are as previously described, reacting a compound of the general formula



wherein X and m are as previously described,

with a compound of the general formula



wherein R<sup>2</sup>, L and n are as previously described and r is an integer from 0 to 4, R<sup>6</sup>, each occurrence, independently, is halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)<sub>k</sub>-(W)<sub>s</sub>-E' or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s'</sub>-E', provided that no more than one of R<sup>6</sup> is -(Q)<sub>k</sub>-(W)<sub>s</sub>-E' or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s'</sub>-E', wherein Q, W, E', C<sub>6</sub>H<sub>4</sub>, k, s', s'' and s''' are as previously described,

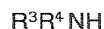
or

(i) for the manufacture of compounds of formula I wherein Y is -O-, f is 1, h is zero, R<sup>1</sup> is propyl, A is -O-B and B is phenyl substituted by the group -CH<sub>2</sub>CH<sub>2</sub>-COR<sup>2</sup> and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)<sub>k</sub>-(W)<sub>s</sub>-E or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s'</sub>-E, provided that no more than one of said substituents is -(Q)<sub>k</sub>-(W)<sub>s</sub>-E or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s'</sub>-E, with -COR<sup>2</sup> being lower alkoxy carbonyl, and the remaining symbols are as previously described, catalytically hydrogenating a compound of formula I wherein Y is -O-, f is 1, h is zero, R<sup>1</sup> is allyl, A is -O-B and B

is phenyl substituted by the group  $-\text{CH}=\text{CH}-\text{COR}^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(\text{Q})_k-(\text{W})_s-\text{E}$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}$ , provided that no more than one of said substituents is  $-(\text{Q})_k-(\text{W})_s-\text{E}$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}$ , with  $-\text{COR}^2$  being lower alkoxy carbonyl, and the remaining symbols are as previously described,

or

(k) for the manufacture of compounds of formula I wherein A is  $-\text{B}$  or  $-\text{O}-\text{B}$ , wherein B is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group  $-\text{COR}^2$ ,  $-(\text{O})_t-(\text{W})_s-\text{COR}^2$  or  $-(\text{CH}=\text{CH})_p-\text{COR}^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(\text{Q})_k-(\text{W})_s-\text{E}$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}$ , provided that no more than one of said substituents' is  $-(\text{Q})_k-(\text{W})_s-\text{E}$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}$ , and wherein E is  $-\text{COR}^2$  and  $\text{R}^2$  is  $-\text{NR}^3\text{R}^4$  and  $\text{R}^3$  and  $\text{R}^4$ , each occurrence, independently, are hydrogen or lower alkyl and the remaining symbols are as previously described, treating a compound of formula I wherein A is  $-\text{B}$  or  $-\text{O}-\text{B}$ , wherein B is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group  $-\text{COR}^2$ ,  $-(\text{O})_t-(\text{W})_s-\text{COR}^2$  or  $-(\text{CH}=\text{CH})_p-\text{COR}^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(\text{Q})_k-(\text{W})_s-\text{E}$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}$ , provided that no more than one of said substituents' is  $-(\text{Q})_k-(\text{W})_s-\text{E}$  or  $-(\text{Q})_k-(\text{W})_s-\text{C}_6\text{H}_4-(\text{W})_s-\text{E}$ , and wherein E is  $-\text{COR}^2$  and  $\text{R}^2$  is hydroxy with an amine of the general formula



wherein  $\text{R}^3$  and  $\text{R}^4$  are as previously described,

and, if desired,

(l) converting a compound obtained into a pharmaceutically acceptable salt.

17. A medicament containing a compound in accordance with any one of claim 1-13 and a therapeutically inert excipient.

18. A medicament for the control or prevention of inflammatory diseases, such as psoriasis, inflammatory bowel diseases, asthma, allergy, arthritis, dermatitis, gout, pulmonary disease, ischemia/reperfusion injury, and trauma induced inflammation, such as spinal cord injury.

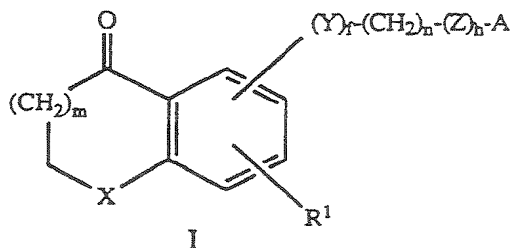
19. The use of a compound in accordance with any one of claims 1-13 in the control or prevention of illnesses.

20. The use of a compound in accordance with any one of claims 1-13 in the control or prevention of inflammatory diseases, such as psoriasis, inflammatory bowel disease, asthma, allergy, arthritis, dermatitis, gout, pulmonary disease, ischemia/reperfusion injury, and trauma induced inflammation, such as spinal cord injury.

21. The use of a compound in accordance with any one of claims 1-13 for the manufacture of medicaments against inflammatory diseases, such as psoriasis, inflammatory bowel disease, asthma, allergy, arthritis, dermatitis, gout, pulmonary disease, ischemia/reperfusion injury, and trauma induced inflammation, such as spinal cord injury.

#### Claims for the following Contracting States : ES, GR

1. A process for the manufacture of compounds of the general formula



wherein

X is -O- or -CH<sub>2</sub>-;

Y is -O-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -C≡C- or -OCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-;

Z is -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -C≡C-;

R<sup>1</sup> is hydrogen, lower alkyl, lower alkenyl, cycloalkyl or aralkyl;

A is -B or -O-B;

B is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group -COR<sup>2</sup>, -(O)<sub>t</sub>-(W)<sub>s</sub>-COR<sup>2</sup> or -(CH=CH)<sub>p</sub>COR<sup>2</sup> and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)<sub>k</sub>-(W)<sub>s</sub>-E or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E, provided that no more than one of said substituents is -(Q)<sub>k</sub>-(W)<sub>s</sub>-E or -(Q)<sub>k</sub>-

(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E;

E is -COR<sup>2</sup> or R<sup>2</sup>;

W is -CR<sup>3</sup>R<sup>4</sup>-;

Q is -O- or carbonyl;

R<sup>2</sup> is hydroxy, lower alkoxy or -NR<sup>3</sup>R<sup>4</sup>;

R<sup>3</sup> and R<sup>4</sup>, each occurrence, independently, are hydrogen or lower alkyl;

f, h, k, m and t, independently, are 0 or 1;

n, s and s', independently, are an integer from 1 to 12;

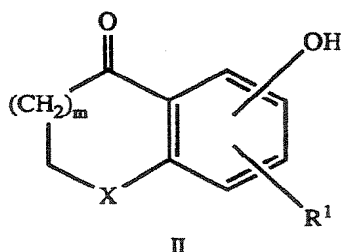
p is an integer from 1 to 2;

s'' and s''', independently, are an integer from 0 to 12; and

C<sub>6</sub>H<sub>4</sub> is a 1,2-, 1,3- or 1,4-phenylene moiety,

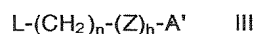
their geometric and optical isomers and, when R<sup>2</sup> is hydroxy, pharmaceutically acceptable salts thereof with bases, which process comprises

(a) for the manufacture of compounds of formula I wherein Y is -O-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy and the remaining symbols are as previously described, reacting a compound of the general formula



wherein X, R<sup>1</sup> and m are as previously described,

with a compound of the general formula

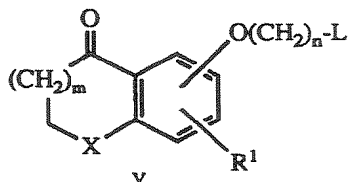


wherein Z, h and n are as previously described, A' is -B' or -O-B', wherein B' is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group -COR<sup>2</sup>, -(O)<sub>t</sub>-(W)<sub>s</sub>COR<sup>2</sup> or

$-(CH=CH)_pCOR^{2'}$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E'$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s'''}-E'$ , provided that no more than one of said substituents is  $-(Q)_k-(W)_s-E'$  or  $(Q)_k-(W)_s-C_6H_4-(W)_{s'''}-E'$ , wherein  $E'$  is  $-COR^{2'}$  or  $R^{2'}$  and  $R^{2'}$  is lower alkoxy and Q, W,  $C_6H_4$ , k, p, s, s', s'', s''' and t are as previously described, and L is a leaving group,

or

(b) for the manufacture of compounds of formula I wherein Y is  $-O-$ , f is 1, A is  $-O-B$  and  $R^2$  in symbol A is lower alkoxy and the remaining symbols are as previously described, reacting a compound of the general formula



wherein X,  $R^1$ , L, m and n are as previously described,

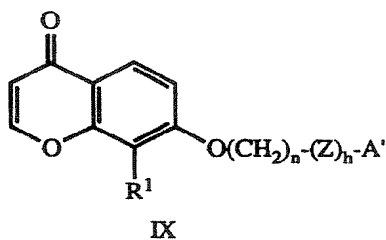
with a compound of the general formula

$HO-B'$

wherein  $B'$  is as previously described,

or

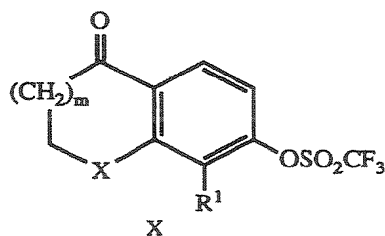
(c) for the manufacture of compounds of formula I wherein X and Y, independently, are  $-O-$ , f and m, independently, are 1 and  $R^2$  in symbol A is lower alkoxy, with  $R^1$  being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, catalytically hydrogenating a compound of the general formula



wherein Z,  $R^1$ ,  $A'$ , h and n are as previously described,

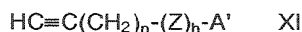
or

(d) for the manufacture of compounds of formula I wherein Y is  $-C\equiv C-$ , f is 1 and  $R^2$  in symbol A is lower alkoxy, with  $R^1$  being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, reacting a compound of the general formula



wherein X, R<sup>1</sup> and m are as previously described,

with a compound of the general formula



wherein Z, A', h and n are as previously described,

or

(e) for the manufacture of compounds of formula I wherein Y is -CH<sub>2</sub>CH<sub>2</sub>-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy, with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, catalytically hydrogenating a compound of formula I wherein Y is -C≡C-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy, with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described,

or

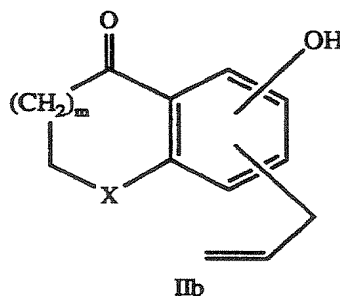
(f) for the manufacture of compounds of formula I wherein Y is -O-, f is 1 and R<sup>2</sup> in symbol A is hydroxy, and the remaining symbols are as previously described, saponifying a compound of formula I wherein Y is -O-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy, and the remaining symbols are as previously described,

or

(g) for the manufacture of compounds of formula I wherein Y is -C≡C- or -CH<sub>2</sub>CH<sub>2</sub>-, f is 1 and R<sup>2</sup> in symbol A is hydroxy with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described, saponifying a compound of formula I wherein Y is -C≡C- or -CH<sub>2</sub>CH<sub>2</sub>-, f is 1 and R<sup>2</sup> in symbol A is lower alkoxy, with R<sup>1</sup> being in 8-position and the side chain in 7-position, and the remaining symbols are as previously described,

or

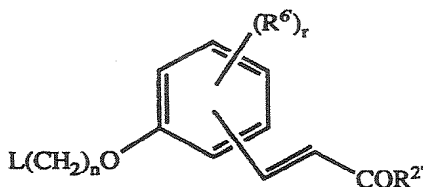
(h) for the manufacture of compounds of formula I wherein Y is -O-, f is 1, h is zero, R<sup>1</sup> is allyl, A is -O-B and B is phenyl substituted by the group -CH=CH-COR<sup>2</sup> and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl, -(Q)<sub>k</sub>-(W)<sub>s</sub>-E or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E, provided that no more than one of said substituents is -(Q)<sub>k</sub>-(W)<sub>s</sub>-E or -(Q)<sub>k</sub>-(W)<sub>s</sub>-C<sub>6</sub>H<sub>4</sub>-(W)<sub>s</sub>-E, with -COR<sup>2</sup> being lower alkoxycarbonyl, and the remaining symbols are as previously described, reacting a compound of the general formula





wherein X and m are as previously described,

with a compound of the general formula



XII

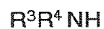
wherein  $R^2$ , L and n are as previously described and r is an integer from 0 to 4,  $R^6$ , each occurrence, independently, is halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E'$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s''}-E'$ , provided that no more than one of  $R^6$  is  $-(Q)_k-(W)_s-E'$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s''}-E'$ , wherein Q, W,  $E'$ ,  $C_6H_4$ , k,  $s'$ ,  $s''$  and  $s'''$  are as previously described,

or

(i) for the manufacture of compounds of formula I wherein Y is -O-, f is 1, h is zero,  $R^1$  is propyl, A is -O-B and B is phenyl substituted by the group  $-CH_2CH_2-COR^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s''}-E$ , provided that no more than one of said substituents is  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s''}-E$ , with  $-COR^2$  being lower alkoxy carbonyl, and the remaining symbols are as previously described, catalytically hydrogenating a compound of formula I wherein Y is -O-, f is 1, h is zero,  $R^1$  is allyl, A is -O-B and B is phenyl substituted by the group  $-CH=CH-COR^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s''}-E$ , provided that no more than one of said substituents is  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s''}-E$ , with  $-COR^2$  being lower alkoxy carbonyl, and the remaining symbols are as previously described,

or

(k) for the manufacture of compounds of formula I wherein A is -B or -O-B, wherein B is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group  $-COR^2$ ,  $-(O)_t-(W)_s-COR^2$  or  $-(CH=CH)_pCOR^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s''}-E$ , provided that no more than one of said substituents' is  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s''}-E$ , and wherein E is  $-COR^2$  and  $R^2$  is  $-NR^3R^4$  and  $R^3$  and  $R^4$ , each occurrence, independently, are hydrogen or lower alkyl and the remaining symbols are as previously described, treating a compound of formula I wherein A is -B or -O-B, wherein B is a mono-, di- or tricyclic aromatic or heteroaromatic moiety substituted by the group  $-COR^2$ ,  $-(O)_t-(W)_s-COR^2$  or  $-(CH=CH)_pCOR^2$  and which may also contain up to 4 additional substituents selected, independently, from the group consisting of halogen, cyano, lower alkyl, lower alkoxy, sulfonamido, alkanoyl, aroyl,  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s''}-E$ , provided that no more than one of said substituents' is  $-(Q)_k-(W)_s-E$  or  $-(Q)_k-(W)_s-C_6H_4-(W)_{s''}-E$ , and wherein E is  $-COR^2$  and  $R^2$  is hydroxy with an amine of the general formula



wherein  $R^3$  and  $R^4$  are as previously described,

and, if desired,

(l) converting a compound obtained into a pharmaceutically acceptable salt.

2. A process according to Claim 1, wherein E is  $-COR^2$ .

3. A process according to Claim 1 or 2, wherein Y is -O-, R<sup>1</sup> is lower alkyl, n is 3-8 and m and f are 1.
4. A process according to Claim 3, wherein Y is -O-, R<sup>1</sup> is lower alkyl, h is 0, m and f are 1, n is 3-8 and A is -O-B, and B is a mono-, di- or tricyclic aromatic moiety.
5. A process according to Claim 1 or 2, wherein Y is -O-, R<sup>1</sup> is lower alkyl or aralkyl, h is 0, m and f are 1, n is 3-8 and A is -B, wherein B is a monocyclic aromatic moiety, preferably phenyl, substituted by -(O)<sub>t</sub> - (W)<sub>s</sub> -COR<sup>2</sup> and -(Q)<sub>k</sub>-(W)<sub>s</sub>-E, wherein E is -COR<sup>2</sup>, Q is -O-, R<sub>2</sub> is hydroxy, t is 0, s is 2, k is 1 and s' is 1 to 12.
6. A process according to Claim 5, wherein X and Y are -O-, R<sup>1</sup> is lower alkyl, h is 0, m and f are 1, n is 3-8 and A is -B, wherein B is a monocyclic aromatic moiety, preferably phenyl, substituted by -(O)<sub>t</sub> - (W)<sub>s</sub> -COR<sup>2</sup> and -(Q)<sub>k</sub>-(W)<sub>s</sub>-E, wherein E is -COR<sup>2</sup>, Q is -O-, R<sub>2</sub> is hydroxy, t is 0, s is 2, k is 1 and s' is 1 to 6.
7. A process according to Claim 1, wherein 2-[(5-carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid is prepared.
8. A process according to Claim 1, wherein 2-(4-carboxybutoxy)-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid is prepared.
9. A process according to Claim 2, wherein 5-(3-carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid is prepared.
10. A process according to Claim 2, wherein 6-(4-carboxybutoxy)-2-[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyloxy]benzenepropanoic acid is prepared.
11. A process according to Claim 1, wherein 2-[(5-carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-(3-phenylpropyl)-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid is prepared.
12. A process according to Claim 2, wherein (E)-3-[5-(3-carboxypropoxy)-2-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]phenyl]-2-propenoic acid.
13. A process for the manufacture of a medicament, particularly to be used in the control or prevention of inflammatory disease, such as psoriasis, inflammatory bowel disease, asthma, allergy, arthritis, dermatitis, gout, pulmonary disease, ischemia/reperfusion injury, and trauma induced inflammation, such as spinal cord injury, which process comprises bringing a compound of formula I set forth in claim 1 or a geometric or optical isomer or a mixture thereof or, when R<sup>2</sup> is hydroxy, a pharmaceutically acceptable salt of such a compound into a galenical dosage form.
14. The use of a compound of formula I set forth in claim 1 or a geometrical or optical isomer or a mixture thereof or, when R<sup>2</sup> is hydroxy, a pharmaceutically acceptable salt of such a compound for the manufacture of medicaments against inflammatory diseases, such as psoriasis, inflammatory bowel disease, asthma, allergy, arthritis, dermatitis, gout, pulmonary disease, ischemia/reperfusion injury, and trauma induced inflammation, such as spinal cord injury.



European Patent  
Office

# PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention  
shall be considered, for the purposes of subsequent  
proceedings, as the European search report

Application Number

EP 92 11 4691

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
A	EP-A-0 292 977 (SEARLE) * page 4 * ---	1,17-21	C07D311/22 C07D311/24 C07D407/12
A	US-A-4 650 812 (N. COHEN et al.) * column 1 * ---	1,17-21	C07D307/83 C07D311/76 C07D405/12
A	EP-A-0 079 637 (FISONS) * pages 1-2; page 18 * ---	1,17-21	C07C57/50 A61K31/35 A61K31/34
A	US-A-3 776 944 (R.E. BROWN et al.) * column 1 - column 2 * -----	1,17-21	A61K31/185
			TECHNICAL FIELDS SEARCHED (Int. Cl. 5)
			C07D C07C
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims</p> <p>Claims searched completely : Claims searched incompletely : Claims not searched : Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search THE HAGUE		Date of completion of the search 07 OCTOBER 1992	Examiner RUSSELL F. ENGLISH
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... @ : member of the same patent family, corresponding document	

EPD FORM 1501 (3.82) (P04/87)



EP 92 11 4691

-C-

Remark: Although claims 19,20  
are directed to a method of  
treatment of the human/animal  
body (Art. 52(4) EPC) the search  
has been carried out and based on  
the alleged effects of the  
compound.